

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

200936USPCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/719554

INTERNATIONAL APPLICATION NO.
PCT/FR99/01513INTERNATIONAL FILING DATE
23 JUNE 1999PRIORITY DATE CLAIMED
23 JUNE 1998

TITLE OF INVENTION

NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY WITH HUMAN ENDOGENOUS
RETROVIRAL MOTIFS, AND THEIR USES

APPLICANT(S) FOR DO/EO/US

Patric M. ALLIEL, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Request for Consideration of Documents Cited in International Search Report

Notice of Priority

PCT/IB/304

PCT/IB/308

Drawings (64 Sheets)

Sequence Listing (84 Sheets)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/719554

INTERNATIONAL APPLICATION NO.

PCT/FR99/01513

ATTORNEY'S DOCKET NUMBER

200936US0PCT

21. The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). ☐ 20 ☒ 30

\$130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	37 - 20 =	17	x \$18.00
Independent claims	6 - 3 =	3	x \$80.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>

\$306.00

\$240.00

\$0.00

TOTAL OF ABOVE CALCULATIONS =

\$1,536.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). ☐

\$0.00

SUBTOTAL =

\$1,536.00

Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). ☐ 20 ☐ 30 +

\$0.00

TOTAL NATIONAL FEE =

\$1,536.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐

\$0.00

TOTAL FEES ENCLOSED =

\$1,536.00

Amount to be:
refunded

\$

charged

\$

☒ A check in the amount of \$1,536.00 to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 15-0030 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



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Surinder Sachar
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SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER

DATE

Dec. 26 2000

PTO/PCT Rec'd 02 JUL 2001

#4

200936US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
PATRICK ALLIEL ET AL : ATTN: APPLICATION DIVISION
SERIAL NO: 09/719,554 :
FILED: December 26, 2000 :
FOR: NUCLEIC SEQUENCE AND :
DEDUCED PROTEIN SEQUENCE :
FAMILY WITH HUMAN :
ENDOGENOUS RETROVIRAL :
MOTIFS, AND THEIR USES :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office Communication mailed April 30, 2001, Applicants submit herewith a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. Prior to examination on the merits, please amend the above-identified application as follows.

IN THE SPECIFICATION

Please amend the specification as follows:

Page 69 (Abstract), after the last line, beginning on a new page, please delete the original Sequence Listing and replace with the substitute Sequence Listing appended herewith.

09/719,554

REMARKS

Claims 1-37 are active in the present application. Applicants have now submitted a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. The sequence information recorded in the corresponding computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing. Support for all of the sequences listed in the substitute Sequence Listing is found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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200936US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
PATRICK M. ALLIEL ET AL : ATTN: APPLICATION DIVISION
SERIAL NO: NEW PCT APPLICATION :
(Based on PCT/FR00/01513)
FILED: HEREWITH :
FOR: NUCLEIC SEQUENCE AND :
DEDUCED PROTEIN SEQUENCE
FAMILY WITH HUMAN
ENDOGENOUS RETROVIRAL
MOTIFS, AND THEIR USES

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend the claims as follows:

3. (Amended) A nucleic acid fragment, characterized in that it comprises a segment of a sequence as claimed in claim 1 [or claim 2] and in particular the sequence SEQ ID NO: 3-22, 28 and 61, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences as well as fragments derived from the coding

regions of the preceding sequences corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

4. (Amended) Transcripts, characterized in that they are generated from the sequences as claimed in [any one of claims 1 to 3] claim 1.

5. (Amended) A diagnostic reagent for the differential detection of complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label.

10. (Amended) A method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the *env* or *env* and *gag* type, their normal or pathological variants, by hybridization and/or gene amplification, carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analyzed is brought into contact with at least one probe as claimed in claim 5[, claim 6 or claim 8,] and

(b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

11. (Amended) The method of detection as claimed in claim 10, characterized in that it comprises:

- prior to step (a):
- a step of preparing the relevant biological tissue or fluid,
- a step of extracting the nucleic acid to be detected, and
- at least one gene amplification cycle carried out with the aid of at least one reagent

[as claimed in any one of claims 5 to 7] selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label, and subsequent to step (b):

- a step of comparing the nucleic sequences obtained in the said biological sample with the human endogenous retroviral sequences SEQ ID NO: 1 or SEQ ID NO:2 or to a sequence exhibiting a level of homology with SEQ ID NO: 1 or SEQ ID NO:2 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains [as claimed in any one of claims 1 to 3], by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a deletion or a single mutation between the various sequences compared.

12. (Amended) A method of detecting the transcripts as claimed in claim 4, characterized in that it comprises:

- collecting messenger RNAs obtained from control biological samples and from a similar sample collected from patients, and

- the qualitative and/or quantitative analysis of the said mRNAs by *in situ*

hybridization, by dot-blot, Northern blotting, RNase mapping or RT-PCR, with the aid of a diagnostic reagent selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label [as claimed in any one of claims 5 to 9].

13. (Amended) Chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence selected from the group consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, associated with an endogenous retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides as claimed in [claims 1 to 4] claim 1.

14. (Amended) A method for the detection and/or evaluation of an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, wherein the sequence are SEQ ID NO: 1 or SEQ ID NO:2 or

to a sequence exhibiting a level of homology with SEQ ID NO: 1 or SEQ ID NO:2 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the *env*-type domains [as claimed in any one of claims 1 to 9], characterized in that it comprises:

- depositing on an appropriate support, cDNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or from specific oligonucleotide sequences, the said DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/ deregulation of motifs belonging to the said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as claimed in claim 13,

- the hybridization of the said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and

- the detection of the hybrids formed.

16. (Amended) The method as claimed in claim 14 [or claim 15], characterized in that the said support comprises, in addition, any endogenous or exogenous retroviral sequence.

17. (Amended) The kit for the detection and/or evaluation of an autoimmune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in addition to the buffers necessary for carrying out a method according to [any one of claims 14 to 16] claim 14:

- diagnostic reagents A selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label [as claimed in any one of claims 5 to 9], and

- reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

19. (Amended) Translational products, characterized in that they are encoded by a nucleotide sequence as claimed in [any one of claims 1 to 4] claim 1.

20. (Amended) A peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO: 1-22, 28 and 61 as claimed in [any one of claims 1 to 4] claim 1.

22. (Amended) The peptide as claimed in claim 20 [or claim 21], characterized in that it is selected from the group consisting of:

- the sequences SEQ ID NO: 23-36;
- the sequence SEQ ID NO: 58;
- a C-terminal fragment of the sequence SEQ ID NO: 26, either from the amino acid 291, or from the amino acid 321, starting from the first methionine of the sequence SEQ ID NO: 26;
- a peptide of the CKS-17/CKS-25 type present in one of the sequences SEQ ID NO: 23-36 or 58; and
- the peptides having affinity with one of the haplotypes of the class I or class II HLA system and in particular the fragments 399-471, 244-271 of enverin, as well as the peptides having the sequence SEQ ID NO: 68-118, in accordance with Table I.

23. (Amended) The peptide as claimed in [any one of claims 20 to 22] claim 20, characterized in that it is obtained from nucleic sequences as claimed in any one of claims 1 to 4, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).

26. (Amended) The composition as claimed in claim 24 [or claim 25], characterized in that said peptide has the sequence SEQ ID NO: 120.

27. (Amended) An antibody, characterized in that it is directed against one or more of the peptides as claimed in [any one of claims 20 to 23] claim 20.

30. (Amended) A method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences as claimed in [any one of claims 19 to 23] claim 19.

31. (Amended) An application of the sequences as claimed in [any one of claims 1 to 9, 13, 14 or 19 to 23] claim 1 to the diagnosis of, to the prognosis of, to the evaluation of genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part of the sequences [as claimed in to any one of claims 1 to 5] in claim 1 and related endogenous or exogenous forms are involved.

32. (Amended) Hybrid nucleic sequences, characterized in that they comprise sequences or motifs as claimed in [any one of claims 1 to 9] claim 1, combined with sequences or motifs of endogenous origin or of exogenous origin or induced exogenously.

33. (Amended) A recombinant cloning or expression vector, characterized in that it comprises a nucleic sequence as claimed in [any one of claims 1 to 4] claim 1.

35. (Amended) A gene therapy vector, characterized in that it comprises all or part of the endogenous retroviral nucleic sequences of the HERV- 7q type as claimed in [any one of claims 1 to 4] claim 1.--

REMARKS

Claims 1-37 are active in the present application. The claims are amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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NUCLEIC SEQUENCE AND DEDUCED PROTEIN SEQUENCE FAMILY
WITH HUMAN ENDOGENOUS RETROVIRAL MOTIFS, AND THEIR USES

5 The present invention relates to a novel
nucleic sequence and deduced protein sequence family
with complete or partial human endogenous retroviral
motifs, and sequences flanking or adjacent to said
sequences, and controlled by the latter; modification
of the expression or impairment of the structure
10 (polyadenylation, alternative splicing and the like) of
said flanking sequences.

The invention also relates to the detection
and/or use of said nucleic sequences and of said
corresponding protein sequences in the context of
15 diagnostic, prophylactic and therapeutic applications,
in particular for neuropathological conditions with an
autoimmune component such as multiple sclerosis.

The invention also relates to the production of
antisense double-stranded and single-stranded nucleic
20 probes, of ribozymes, capable of modulating viral
replication (T.R. Cech, *Science*, 1987, **236**, 1532-1539;
R.H. Symons, *Trends Biochem. Sci.*, 1989, **14**, 445-450)
of the corresponding recombinant molecules, and
associated antibodies.

25 Retroviruses are viruses which replicate solely
by using the opposite route to the conventional
processing of genetic information. This process, called
reverse transcription, is mediated by an RNA dependent
DNA polymerase or reverse transcriptase, encoded by the
30 *pol* gene. Retroviruses also encode at least two
additional genes. The *gag* gene encodes the proteins of
the skeleton, matrix, nucleocapsid and capsid. The *env*
gene encodes the envelope glycoproteins. Retroviral
transcription is regulated by promoter regions or
35 "enhancers" situated in highly repeated regions or LTR
(*Long Terminal Repeat*) and which are present at both
ends of the retroviral genome.

During the infection of a cell, polymerase
makes a DNA copy of the RNA genome; this copy may then

integrate into the human genome. Retroviruses do not kill the cells which they infect, but on the contrary often enhance their rate of growth. Retroviruses can infect germ cells or embryos at an early stage; they
5 can, under these conditions, integrate the germ line and be transmitted by vertical Mendelian transmission, which constitutes the closest relationship between a host and its parasite. These endogenous viruses can degenerate during generations of the host organism and
10 lose their initial properties. However, some of them may conserve all or part of their properties or of the properties of their constituent motifs, or acquire novel functional properties having an advantage for the host organism, which would explain the preservation of
15 their sequence.

The existence of endogenous motifs having long open reading frames and/or subjected to a strong selection pressure can therefore be an indication of a preserved or acquired biological function, which may
20 correspond to a benefit for the host organism. These retroviral sequences can also undergo, over the generations, discrete modifications which will be able to trigger some of their potentials and generate or promote pathological processes. It has recently
25 appeared necessary to carry out a review and to identify these sequences so as to be able to evaluate their functional impact.

Human endogenous retroviral sequences or HERVs represent a substantial part of the human genome. These
30 retroviral regions exist in several forms:

- complete endogenous retroviral structures combining *gag*, *pol* and *env* motifs, flanked by repeat nucleic sequences which exhibit a significant analogy with the LTR-*gag-pol-env*-LTR structure of infectious
35 retroviruses,

- truncated retroviral sequences; for example the retrotransposons lack their *env* domain and the retroposons do not possess the *env* and LTR regions.

Up until now, the study of these regions of the genome has been neglected in humans for essentially two reasons:

- the existence of insertions/deletions which can shift the reading frame and of mutations which modify the sequence. These modifications cause impairment of the structure and consequently of the biological function of these motifs,
- the absence of confirmed associations with human pathological conditions.

The recent knowledge of fragments which are significantly representative of the human genome and an orientation of research studies toward a study of structure/function of endogenous retroviral motifs have made it possible to specify the importance of these regions. The involvement of truncated or complete endogenous sequences in pathological conditions in animals is documented; for example their association with tumor processes has been clearly demonstrated (S.K. Chattopadhyay et al., 1982, *Nature*, 295, 25-31). Research aimed at specifying the association or the influence of HERVs in human pathological conditions is now therefore justified.

A classification of the HERV elements has been proposed (Tönjes R.R. et al., *AIDS & Hum. Retroviral.*, 1996, 13, p261-p267; A.M. Krieg et al., *FASEB J.*, 1992, 6, 2537-2544). It is based on a homology of these sequences with retroviruses isolated in animals, with the aid of heterologous retroviral probes. Indeed, in general, the HERVs exhibit relatively little homology with known human infectious retroviruses.

The class I families exhibit a sequence homology with the type C mammalian retroviruses; there may be mentioned in particular the ERI superfamily, close to the MuLV virus (*murine leukemia virus*) and to the BaEV virus (*baboon endogenous virus*).

The class II families exhibit a sequence homology with the type B mammalian retroviruses such as

MMTV (mouse mammary tumor virus) or the type D retroviruses such as SRV (squirrel monkey retrovirus).

Other families have also been described; among these, there may be mentioned HERVs which exceptionally exhibit partial homology with HTLV-1 (RTVL-H) or primate viruses; HRES-1, for example, exhibits sequence homology with HTLVs.

Programmes for very large sequencing of the human genome now make it possible to have available a significant number of novel retroviral sequences. The use of data processing software packages makes it possible to identify and analyse these genes. In this context, a systematic search relating to the entire information available to date has been initiated in order to identify novel human endogenous retroviral sequences as a function of certain analytical criteria:

- presence of long open reading frames conserved during evolution of the host organism and which may suggest a biological function,
- analogy with sequences already characterized outside or inside the retrovirus domain,
- location in regions of susceptibility for certain pathological conditions or close to essential genes, for example in the cancer domain, regulation of the immune system or in certain neuropathological conditions.

The work carried out by the inventors on sequence databases allowed them to identify a set of endogenous retroviral sequences or motifs whose normal or pathological expression can promote or disrupt a protective effect in relation to pathological processes, or play a role in the onset or worsening of pathological conditions.

The subject of the present invention is a purified nucleic acid fragment, characterized in that it comprises all or part of a sequence encoding a human endogenous retroviral sequence, which has at least env-type retroviral motifs, corresponding to the sequence SEQ ID NO: 1 or to a sequence exhibiting a level of

homology with said sequence SEQ ID NO: 1 greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the env-type domains.

5 The expression homologous sequence is understood to mean both a sequence which exhibits complete or partial identity with the abovementioned sequence SEQ ID NO: 1 and a sequence which exhibits partial similarity with said sequence SEQ ID NO: 1.

10 According to an advantageous embodiment of said fragment, it has retroviral motifs corresponding to an env domain and corresponding to the sequence SEQ ID NO: 1 and retroviral motifs corresponding to a gag domain and corresponding to the sequence
15 SEQ ID NO: 2 or to a sequence exhibiting a level of homology greater than or equal to 80% on more than 190 nucleotides or greater than or equal to 70% on more than 600 nucleotides for the env-type domains and a level of homology greater than or equal to 90% on more
20 than 700 nucleotides or greater than or equal to 70% on more than 1 200 nucleotides for the gag-type domains, said motifs having no insertion or deletion of more than 200 nucleotides.

 Said fragments constitute a novel family of
25 human endogenous retroviral sequences (HERV-7q family) which exhibits sequence homology with the MSRV retroviruses, as described in International Application WO 97/06260; said fragments according to the present invention have:

30 - two repeat nucleotide motifs of 711 bp (Figure 3), having characteristic signals identified in LTRs (*Long Terminal Repeats*): transcription promoters of the TATAA or CCAAT box type. These repeat domains delimit three deduced motifs of the gag, pol and env
35 type (Figure 2),

 - an env-type motif (positions 6965 nt - 9550 nt on the sequence SEQ ID NO: 3 or in Figure 1) which contains a long open reading frame of 1 620 nucleotides (positions 7874-9493 of the sequence

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ID NO: 3 and Figure 1) encoding a protein having an unpublished sequence of 540 amino acids called enverin (Figure 4 and SEQ ID NO: 26) and underlined fragment in Figure 18. There is present inside the transmembrane domain of this env domain a peptide motif of the CKS-25/CKS-17 type (Figure 5), recognized as having immunosuppressive functions on the host lymphocytic cells (M. Mitani et al., 1987, *Proc. Natl. Acad. Sci. USA*, **84**, 237-240). A zinc finger type domain **HX₃₋₄HX₂₂₋₃₃CX₂C** (Kulkolski et al., 1992, *Mol. Cell. Biol.*, **12**, 2331-2338), which is present in integrase-type domains is identified in another reading frame. This particular env domain signatures the characteristic of novel endogenous retroviral motifs,

the motif (positions 3065 nt - 4390 nt on the sequence SEQ ID NO: 3) of the gag type encoding protein motifs according to Figure 6 (SEQ ID NO: 58) (positions 3118-4198 of SEQ ID NO: 3) was identified by virtue of analogies with known gag domains. The region of major homology **QX₃EX₇R** is for example present (Benit et al., 1997, *J. Virol.*, **71**, 5652-5657). The nucleic acid binding motif **CX₂CX₃₋₄HX₄C**, situated at the C-terminal position, is identified in another reading frame (Covey et al., 1986, *Nucleic Acids Res.*, **14**, 623-633). Upstream of the gag domain, a motif of 182 nucleotides is detected which is repeated twice (Figure 1),

- the pol domain exhibits the conventional consensus of a retrovirus pol region at the level of the protease, reverse transcriptase and RNase H domains. A motif close to the consensus **LLDTGA** is found in pol (Weber et al., 1988, *Science*, **243**, 928-931). The motifs **D** and **AF**, **LPQ** and **SP**, and **YVDD** (Xiong and Eickbush, 1990, *EMBO J.*, **9**, 3353-3362) are respectively found in the 3rd, 4th and 5th homology boxes. The motifs **YTDGSS** and **TDS** are present in the RNase H region,

- the gag and pol regions could be considered as being joined with a passage from the gag region to the pol region by a reading frame shift.

The present invention includes the sequences belonging to the HERV-7q family as defined above (presence of the SEQ ID NO: 1 sequence or of a homologous sequence or presence of both the sequences
5 SEQ ID NO: 1 and SEQ ID NO: 2) and in particular the sequences SEQ ID NO: 3-22, 28 and 61; it also includes the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences as well as fragments derived from the coding regions of
10 the preceding sequences corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences (SEQ ID NO: 37-57, 59-60 and 121-122).

These various fragments may be advantageously
15 used as primers or as probes (reagents A); they hybridize specifically under high stringency conditions to a sequence of the HERV-7q family.

Among these fragments, the following fragments may be preferably mentioned:

20 - a fragment of 182 nucleotides, repeated twice, situated upstream of the gag domain at positions 2502-2611/2613-2865 of SEQ ID NO: 3:

Primers and probes specific for the gag region

- a sense primer G1F located in the region
25 upstream of the gag domain of HERV-7q:
5'GGACCATAGAGGACACTCCAGGACTA3' (SEQ ID NO: 37);

- an antisense primer G1R located in the terminal 3' region of the gag domain:
5'CCTCAGTCCTGCTGCTGGATCATCT3' (SEQ ID NO: 38)

30 - the fragment of 1505 nt amplified by the pair G1F-G1R is used in order to generate the probes capable of hybridizing the various PCR amplification products:

- a nested sense primer G2F: (SEQ ID NO: 39)

5'CCTCCAAGCAGTGGGAGGAAGAGAATT3'

35 - a nested antisense primer G2R: (SEQ ID NO: 40)

5'CCTTCCCTGTGTTATTGTGGACATCATT3'

- a nested sense primer G4F: (SEQ ID NO: 41)

5'GGAAGAAGTCTATGAATTATTCAATGATGT3'

- a nested sense primer G3F: (SEQ ID NO: 42)

5'GGGACACAGAATCAGAACATGGAGATT3'

- a nested antisense primer G4R: (SEQ ID NO: 43)

5'GCCTTCAGAAGAGTCAGGTGACAGAGA3'

- a nested antisense primer G5R: (SEQ ID NO: 44)

5'GAGCCTCCAAAGTCCACTTGCCTGA3'

Primers and probes specific for the env region

- a sens primer E1F: (SEQ ID NO: 45)

5'GATTTTCAGTATCTACTAGTCTGGGTAGAT3'

- an antisense primer E1R: (SEQ ID NO: 46)

5'CTAGGAAATCCAGCTAGTCCTGTCTCA3'

- the fragment of 2529 nt, amplified by the pair of primers E1F-E1R, is used to generate the probes capable of hybridizing the various PCR amplification products:

- a sense primer E2F: (SEQ ID NO: 47)

5'CCAAGACAGCCAAGTTAGTTGCAGACAT3'

- an antisense primer E2R: (SEQ ID NO: 48)

5'GGACGCTGCATTCTCCATAGAACTCTT3'

- a sense primer E3F: (SEQ ID NO: 49)

5'GCAATACTACATACACAACCAACTCCCAA3'

- an antisense primer E3R: (SEQ ID NO: 50)

5'GGGGGAGGCATATCCAACAGTTAGTA3'

- a sense primer E4F: (SEQ ID NO: 51)

5'CCATCTACACTGAACAAGATTTATACACTT3'

- an antisense primer E4R: (SEQ ID NO: 52)

5'AATGCCAGTACCTAGTGCACCTAGCACT3'

- a sense primer E5F: (SEQ ID NO: 53)

5'CGAATACAACGTAGAGCAGAGGAGCTTCGAA3'

- a sense primer E6F: (SEQ ID NO: 54)

5'AGCCCAAGATGCAGTCCAAGACTAAGAT3'

- a primer E5R: (SEQ ID NO: 55)

5'GCGTAGTAGAGGTTGTGCAGCTGAGAT3'

- a primer ExF: (SEQ ID NO: 56)

CCCTTACCAAGAGTTTCTATGGAGAAT

- a primer ExR: (SEQ ID NO: 57)

ACCGCTCTAACTGCTTCCTGCTGAATT

All the oligonucleotides are designed to be able to generate a sense primer and an antisense primer by a shift in the sequence of the reference primer of 1 to 7

nucleotides toward the 5' side or toward the 3' side; the modification of the sequence may cause a modification of the size of the primer of 1 to 7 nucleotides depending on the cases. The primers chosen
5 may be optimized depending on the cases by shortening or extension affecting 1 to 9 nucleotides.

Preferably, the hybridization, cloning, subcloning, production, preparation and analysis of the nucleic acids, peptides and antibodies, the sequencing
10 of the nucleic acids and peptides, the *in situ* hybridization and the immunohistochemistry are carried out under the conditions described in the following books:

- Current Protocols in Molecular Biology, Eds.
15 F.M. Ausubel, R. Brent & R.E. Kingston et al. Green Publishing associates and Wiley Interscience.

- Molecular Cloning: a laboratory manual. Eds. J. Sambrook, E.F. Fritsch & T. Maniatis, Cold Spring Harbor Laboratory Press, Cold Spring Harbor.

20 - The Practical Approach series. Eds. D. Rickwood & B.D. Ames, IRL Press and Oxford University Press. In particular antibodies I & II; DNA cloning I, II, III; Nucleic acid and protein sequence analysis; Nucleic acid hybridization; Nucleic acid
25 sequencing; Oligonucleotide synthesis; Protein purification applications; Protein purification methods; Protein sequencing; Transcription and translation; Gels electrophoresis of nucleic acids; Gels electrophoresis of proteins; Genome analysis; HPLC
30 of macromolecules; Human genetic diseases; Microcomputing in biology; Molecular neurobiology; Mutagenicity testing; Essential molecular biology I & II.

- Proteome research: New frontiers in
35 functional genomics, Eds. M.R. Wilkins et al., Springer.

The human endogenous retroviral sequence (SEQ ID NO: 3) situated on the long arm of chromosome 7 corresponds to the HERV-7q sequence; it has 10.5 kb

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(Figs. 1 and 2) and satisfies the criteria defined above.

The search for domains exhibiting total or partial similarity with the *gag* and *env* regions of
5 HERV-7q resulted in the identification of novel endogenous retroviral sequences. These sequences may have the structure of a complete endogenous retrovirus such as the endogenous retroviral sequence situated close to the gene for the alpha and delta subunits of
10 the T cell receptor, and consequently called HERV-TcR; by way of example, Figure 7 shows the comparison of the nucleic alignments of the respective *gag* domains of HERV-7q and HERV-TcR (sequence HG12, SEQ ID NO: 19). Partial retroviral structures also exist. These
15 retroviral domains, similar to HERV-7q, are identified in independent nucleic sequences as shown by their chromosomal location. Nucleic motifs (called here HEx or HGx, and analogous to *env* or *gag* type domains, respectively) resembling the *env* or *gag* domains of
20 HERV-7q were found, with the aid of the abovementioned databases:

- HE2: chromosome 17 (SEQ ID NO: 4),
- HE3 and HG3: chromosome 6 (SEQ ID NO: 5 and 6),
- HE4: chromosome X (SEQ ID NO: 7),
- 25 - HE5: chromosome X q22 (SEQ ID NO: 8),
- HE6 and HG6: chromosome 1 q23.3-q24.3 (SEQ ID NO: 9 and 10),
- HE7: chromosome 7 p15 (SEQ ID NO: 11),
- HE8 and HG8: chromosome 19 (SEQ ID NO: 12 and
30 13),
- HE9: chromosome X (SEQ ID NO: 14),
- HE10: chromosome X q13.1-21.1 (SEQ ID NO: 15),
- HE11 and HG11: chromosome 7 q21-22 (SEQ ID NO: 16 and 17),
- 35 - HE12 and HG12, in HERV-TcR: chromosome 14 q11.2 (SEQ ID NO: 18 and 19),
- HE13 (SEQ ID NO: 61): chromosome 6 q24.1-24.3

The present invention also includes the coding and noncoding fragments for all or part of enverin

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comprising at least 14 nucleotides and in particular the fragments encoding the C-terminal part of enverin, either from amino acid 291, or from amino acid 321, starting from the first methionine.

5 These fragments comprise in particular a critical zone where two inserts of 12 nucleotides were characterized:

 - a first insert was identified (sequence A) in individuals of 2 groups (patients and controls). This
10 insert, situated between amino acids 487 and 488, makes it possible to insert the tetrapeptide VLQM. A comparative analysis shows that this insert is identified in a homologous region situated in the
15 sequence HE13, belonging to the HERV-7q family. The amplification of the HE13 type sequence could indicate that there is an impairment of the enverin sequence of HERV-7q, which would promote the amplification of the sequence contained in HE13. This observation also makes
20 it possible to use this insert as a specific element for amplification of sequences of the HE13 type.

 A second insert (sequence B) was identified in a patient with MS. The insert of 12 nucleotides is situated at the level of amino acid 495 and encodes the tetrapeptide MQSM. It is remarkable to observe that
25 this insert is also identified in a homologous region situated in HE13.

 Sequence A: TAAACTACAAATGGTTCTTCAAATGGAGCCCA
(SEQ ID NO: 59)

 Sequence B: GATGCAGTCCAAGATGCAGTCCATGACTAAGA
30 (SEQ ID NO: 60).

 These observations demonstrate modifications of the enverin sequence of the HERV-7q type which constitute the basis for a detection strategy by allele-specific amplification (AS-PCR), making it
35 possible to detect these differences in a population and which could correspond either to a mutation/deletion associated with a degree of susceptibility, or to a polymorphism, or to a

mutation/deletion associated with a pathological condition such as multiple sclerosis.

The alignments of the *env* (Fig. 8) and *gag* (Fig. 9) domains explain the levels of homology
5 observed between the sequences described above and the homologous sequences in HERV-7q. The analogies can extend to the flanking retroviral motifs.

Analysis of the sequence tags available in databases shows that transcripts belonging to some
10 members of this family, in particular HERV-7q, are essentially expressed in tissues of foetal or placental origin.

Polypeptide sequences generated by these transcripts can therefore be potentially produced and
15 biological functions or activities can be envisaged, by analogy with biologically active polypeptides of viral or retroviral origin; for example, the peptide motifs of the CKS-17 type (Haraguchi et al., PNAS, 1995, 92, 5568-5571) (Fig. 5) or CKS-25 type (Huang S.S. and
20 Huang J.S., J. Biol. Chem. 1998, 273, 4815-4818) which have immuno-modulatory functions on the lymphocytic host cells. The differences in sequence which are observed and possible normal or pathological modifications are in particular responsible for
25 modulation of the function.

HERV-7q represents the paradigm of the novel family of human endogenous retroviral sequences or of endogenous retroviral motifs.

HERV-7q and some of the endogenous retroviral
30 sequences belonging to its family have a *pol*-type domain analogous to *pol*-type retroviral sequences such as for example the *pol* region identified in the MSRV retrovirus associated with multiple sclerosis and described by H. Perron et al. (1997, *Proc. Natl. Acad. Sci. USA*, 94, 7583-7588; International Application PCT
35 WO 97/06260).

However, the sequences according to the present invention are distinguishable from the infectious exogenous retroviral sequences analogous to MSRV

previously described in that the gag and env sequences according to the invention are significantly different according to the criteria defined above and as a function of certain specific characteristics, for example the long open reading frame of the env domain of HERV-7q; they would be able to allow the signaturing of a pathological condition when they have insertions, deletions, reading frame shifts or mutations.

Indeed, the differences observed between the human sequences of the HERV-7q type, which are isolated from individuals reputed to be normal, and the sequences derived from some samples of pathological origin are not randomly distributed. Comparisons carried out between the gag region obtained from infectious retroviral particles (EMBL accession No.: A60168, A60200, A60201, A60171 and the like) and the corresponding gag sequence of HERV-7q (Fig. 9), make it possible to observe that the mutations preferably affect non-sense codons. For example, two non-sense codons in HERV-7q are replaced by an arginine codon in A60200, which makes it possible to obtain a deduced sequence of 109 amino acids for HERV-7q and of 166 amino acids for A60200. The base changes consequently make it possible to extend the reading frame and to potentially encode larger sized polypeptide structures (Figure 10).

Likewise, an env-type sequence obtained from infectious retroviral particles exhibits a significant analogy with the env domain of HERV-7q (Figure 11). These marked analogies between exogenous and endogenous retroviral sequences could be responsible for the triggering or worsening of certain pathological processes, in particular certain autoimmune diseases such as multiple sclerosis. In this regard, it is possible to note that certain endogenous retroviral sequences described in the invention are situated close to or in regions reputed to exhibit susceptibility for multiple sclerosis: for example HERV-7q and the 7q21-22 region of chromosome 7, likewise for HE12 and HG12 in

HERV-TcR and the region of the gene encoding the alpha and delta chains of the T cell receptor, HE2 and chromosome 17, or HE3, HE13 and HG3 and chromosome 6, for example, the sequences HE11 and HG11, around the
5 region 7q 21-22 or HE4, HE5, HE6, HE9, HE10 or HG10 on the X chromosome. These sequences would therefore be capable of providing the means for locating or identifying the genes for predisposition.

No significant homology is observed with
10 endogenous retroviral sequences already described; on the other hand, a limited homology may be noted, which makes it possible to identify a general structure of the env domain; however, said homology is less than the criteria defined according to the invention between the
15 env domains of the sequence HERV-7q (SEQ ID NO: 1) and the sequence HERV-9 (Figure 12). Figure 11 shows extensive homologies between the sequence HERV-7q with an exogenous retroviral sequence (accession No. EMBL: A60170).

20 The human endogenous retroviral sequences belonging to the HERV-7q family can protect against attacks linked to the environment or can be beneficial for the individual. This beneficial effect could be one of the possible reasons for the selection pressure
25 exerted on some of these sequences and the potentially functional character of the deduced protein structures identified: for example the long open reading frame capable of encoding a novel protein and corresponding to the env domain of HERV-7q.

30 The human endogenous retroviral sequences belonging to the HERV-7q family could be associated, for example, with pathological conditions related to processes linked to cancer, to neuropathological conditions with an autoimmune component or to any other
35 pathological process in association or otherwise with endogenous or exogenous viruses or retroviruses. Their action could be related to the outbreak, the worsening, the modification of the time of appearance or the protection against the disease.

In the context of application to autoimmune pathological conditions (such as for example lupus, Sjögren's syndrome, rheumatoid arthritis, multiple sclerosis and the like), significant analogies may be
5 detected between the endogenous retroviral motifs identified and motifs found in retroviral structures characterized in patients with autoimmune pathological conditions such as multiple sclerosis; for example, fragments of gag domain (recently available in
10 databases) obtained from infectious retroviral particles or the complete sequence of the pol domain corresponding to the MSRV virus associated with multiple sclerosis. These retroviral motifs possess significant analogies with homologous endogenous
15 sequences of the HERV-7q type, which makes it possible to envisage direct or indirect association with pathological processes, including multiple sclerosis, in association or otherwise with MSRV.

The importance of these sequences goes beyond
20 the context of autoimmune diseases. Apart from the general importance of retroviral motifs in the triggering or worsening of a tumor process, which is well established in particular in murine models (H. Fan in *The retroviridae*, 1994, ed. J.A. Levy, Plenum, New
25 York, p. 313-353), these sequences could be present close to or inside important genes and could alter the expression thereof: for example HERV-TcR and the genes for the alpha and delta subunits of the receptor for the T cells involved in disruptions of the immune
30 system.

The present invention includes, in addition, the use of sequences combined with the sequences of the HERV-7q family for the detection and/or prognosis of various autoimmune diseases (neuropathological
35 conditions in particular); these sequences encode all or part of a factor whose function, the regulation/de-regulation or alteration (polyadenylation, alternative splicing), is associated with the normal or pathological expression or with the regulation/de-

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regulation of the motifs belonging to the HERV-7q family and correspond to transcripts or cDNAs of the nucleotide sequences encoding genes situated in regions flanking or delimiting retroviral sequences of the
5 HERV-7q family.

The expression flanking region is understood to mean any region situated close to (contained in or including) an endogenous retroviral sequence belonging to the HERV-7q family, as defined above, up to and
10 including the genes immediately contiguous and/or situated at a distance which cannot exceed 120 kb.

The inventors have now found that the presence of the retroviral sequences as defined above disrupts the expression or impairs the structure of the flanking
15 sequences defined below.

The transcripts of said flanking sequences (and fragments thereof, in particular those underlined or in italics in Figures 14-16, 22-26, as defined below:

- at 1021 bp upstream of HERV-7q, there is
20 identified an endogenous retroviral sequence called RH7 (SEQ ID NO: 62 and Figure 22); this sequence is situated in 5' of the HERV-7q sequence; in Figure 22, the portion in italics corresponds to the beginning of the HERV-7q sequence; the RH7 sequence is underlined;
25 two putative polyadenylation sites are in bold. This sequence SEQ ID NO: 62 exhibits significant homology, on more than 6 kb, with RGH-type endogenous retroviral sequences (Figure 13). Sequences belonging to this family are expressed in particular in patients with
30 rheumatoid osteoarthritis (Nakagawa et al., (1997), Arthritis, Rheum., 40, 627-638). The present invention also includes fragments of the sequence SEQ ID NO: 62, comprising between 14 and 50 nucleotides (used as primers), preferably between 14 and 25 nucleotides, or
35 at least 25 nucleotides (used as probe), which fragments have the following characteristics: the 4 nucleotides of the 3' end are different from the corresponding motifs of the sequence RGH2 (bottom sequence in Figure 13, GenBank accession No.: D110 18),

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at less than 9 kb upstream of HERV-7q, there is identified the sequence RAM75 (SEQ ID NO: 63 and Figure 14) containing the 24 coding exons (which cover close to 41 kb) of the gene for peroxisomal ATPase PEX1. PEX1, in combination with PEX6, is responsible for the import of peroxisomal proteins and for stabilizing the PEX5 receptor. A disruption/alteration affecting PEX1 is responsible for various neuropathological conditions such as Zellweger syndrome, neonatal adrenoleukodystrophy and the infantile form of Refsum's disease (Reuber et al., (1997), Nature Genet., 17, 445-448). It can be recalled that the main function of the peroxisomes is associated with the metabolism of fatty acids, in particular by β -oxidation processes. Impairment of the gene identified in the sequence RAM75, or of its expression, by modification of the function of the regulatory 5' and 3' regions or by modification of the splicings or of the polyadenylation processes, in particular under the influence of neighboring retroviral motifs, would be able to disrupt the expression and the structure of ATPase and consequently to disrupt one of the peroxisomal functions, in particular the metabolism of lipids, in particular myelin lipids, with consequences for certain pathological conditions, including neuropathological conditions such as multiple sclerosis; the underlined portions (Figure 14) correspond to the 24 coding exons.

The present invention also includes the fragments of the sequence SEQ ID NO: 63, included in the abovementioned 24 coding exons and comprising at least 14 nucleotides.

Analysis of the expression profile (transcripts and proteins) of the sequence RAM75 (SEQ ID NO: 63) is a good indicator for the differential diagnosis of neuropathological conditions with an autoimmune component.

In Figure 14, the coding exons are underlined. The initiation and non-sense codons as well as the

putative polyadenylation sites are in bold and underlined;

- at 0.7 kb downstream of the sequence HERV-7q and on nearly 17 kb (SEQ ID NO: 64 and Figure 15), there is identified the nucleotide sequence RAV73, where there are detected sequence tags and potential exons capable of producing one or more polypeptide sequences; the invention also includes fragments of this sequence SEQ ID NO: 64 included in the sequence tags and the potential exons as they appear (portions underlined) in Figure 15, which fragments comprise at least 14 nucleotides,

- at 120 kb upstream of the sequence HG3, and on 15 kb, there is the nucleotide sequence RBP3 (SEQ ID NO: 65 and Figure 23), which covers the 3' end of the gene encoding a transcription factor of the Blimp-1 family (SEQ ID NO: 119 and Figure 25), a protein of 789 amino acids which is a repressor of the expression of the interferon-beta gene (Keller and Maniatis, Genes Dev., (1991), 5, 868-879), which is already associated with certain malignant pathological conditions (Mock et al., Genomics, (1996), 37, 24-28), and which could play a role in the differentiation and the pathogenesis of B cells. The possible association of the endogenous retroviral sequence containing the motifs HG3 and HE3 and of Blimp-1 has many benefits, in the case of pathological conditions, and in particular multiple sclerosis. Blimp-1 acts in particular on the B cells whose contribution in inflammatory processes associated with multiple sclerosis is known. Blimp-1 is capable of blocking the viral induction of the INF β promoter whose capacity to reduce the frequency of attacks and the progression of lesions in patients with MS is known. Disruption in the expression or the structure of Blimp-1, in relation to a retroviral element of the HERV-7q type, is consequently associated with neuropathological conditions or with diseases having an autoimmune character, such as multiple sclerosis; this nucleotide sequence RBP3 (SEQ ID

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NO: 65) contains nucleotide motifs identified in the nucleic sequence encoding the Blimp-1 gene; the invention also includes the detection of the mRNA sequences for the Blimp-1 protein (SEQ ID NO: 119),

5 - the endogenous retroviral sequence of the
HERV-7q type, containing HE3 and HG3, is situated in
the HI3 region corresponding to an intron extending
over more than 46 kb (SEQ ID NO: 66), of a gene which
could encode the analogue of APS (Figure 24), a protein
10 of 275 amino acids specific to apoptosis, overexpressed
in various cells in culture after triggering an
apoptotic process (Hammond et al., FEBS Lett., (1998),
425, 391-395). The intron is situated at the level of
amino acid 231 of APS. The end of HE3 is at more than
15 12 kb from the 5' end of the intron, whereas HG3 is
situated at more than 28 kb from the 3' end of the
intron. Apoptotic processes are associated with
multiple sclerosis. In particular, there has been
described an apoptotic process affecting astrocytes and
20 oligodendrocytes in the presence of a purified fraction
of cerebrospinal fluid of patients suffering from
multiple sclerosis (Ménard et al., J. Neurol. Sci.,
(1998), 154, 209-221).

Finally, it should be stressed that the nucleic
25 region containing HE3, HG3, HI3 and RBP3 is located at
the level of the short arm of chromosome 6, in 6p21,
which is a proposed region of susceptibility to
multiple sclerosis (The Multiple Sclerosis Genetic
Group, Nature Genet., (1996), 13, 469-472).

30 The interaction between the HERV-7q type
sequences and the flanking sequences and the importance
of establishing a profile of expression including one
or more of the abovementioned sequences in order to
establish a differential diagnosis of a neuro-
35 pathological condition is even more evident because it
is observed that the sequences HG12 and HE12 are
situated in an intron region of the gene encoding the
alpha and delta subunits of the T cell receptors. The T
cell receptors are involved in the immune regulation

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process and their influence has been proposed in the case of autoimmune diseases, including multiple sclerosis.

The subject of the invention is also
5 transcripts generated from the abovementioned sequences as well as those optionally exhibiting modifications in the reference sequences described in the invention when they are expressed in certain patients.

Indeed, the systems for regulating the the
10 expression of the retroviral proteins of HERV-7q, which are present in the LTR type motifs, could influence the expression of genes situated in the close or distant chromosomal vicinity and could induce disruptions of an immunological and/or neurological character. For
15 example, the endogenous retroviral sequence HERV-TcR exists in the immediate vicinity of the genes for the alpha and delta subunits of the T cell receptor previously described. The LTR-type motifs could also encode superantigens (Acha-Orbea and Palmer, 1991,
20 *Immunol. Today*, 12, 356-361). In general, retroviral proteins of the HERV-7q or related type, or their truncated or partial forms could be involved in cytotoxicity or superantigenicity phenomena, such as for example those derived from the long open reading
25 frame identified in the env domain (Figure 4).

Sequences of the HERV-7q 5' and 3' LTR type, which are highly conserved, are involved in such regulatory effects. By way of example, LTX is described, which is a sequence comparable to that of an
30 HERV-7q LTR (SEQ ID NO: 67 and Figure 16), and which is present in the center of an intron of more than 49 kb, but at 2 kb from the donor 5' site of the FMR2 gene associated with fragile X and encoding a protein of 1311 amino acids (Figure 26). The LTRs modulate the
35 alternative splicing (Kapitonov and Jurka, (1999), *J. Mol. Evol.*, 48, 248-251), the expression of the gene, the binding to nuclear proteins (Akopov et al., (1998), *FEBS Lett.*, 421, 229-233), or allow the

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production of an alternative polyadenylation signal (Goodchild et al., (1992), *Gene*, 121, 287-294).

In general, there may be noted the existence of several endogenous retroviral sequences of the HERV-7q type (HE4, HE5, HE9, HE10), situated at the level of chromosome X which represents the chromosome associated with the largest number of pathological conditions.

In this regard, it is possible to note that retroviral motifs derived from defective regions are capable of having biological functions; for example, the envelope protein p15E, derived from defective retroviral motifs, possesses an anti-inflammatory and immunosuppressive activity (Snyderman and Ciancolo, 1984, *Immunol. Today*, 5, 240-244).

These structures are probably capable of causing breaks or of amplifying deregulations in the immune defense processes. Some of the motifs of the *gag*, *env* and LTR-type domains may be associated with a particular function or may contribute to the normal or pathological function of the flanking domains as defined above (SEQ ID NO: 62-67). Recombinations with an element of exogenous, retroviral origin or otherwise can give rise to the production of nucleic or protein motifs which could either protect or trigger or promote or worsen a pathological condition. Likewise, a retroviral structure containing endogenous retroviral elements according to the invention would be capable of causing a pathological process after passing through an exogenous transient cycle followed by reintegration into a sensitive or critical region of the human genome.

It is thus possible to obtain expression profiles (transcripts and optionally proteins) which correspond to the abovementioned neuropathological conditions.

Likewise, the combination of motifs belonging to the HERV-7q family, or of elements induced by motifs belonging to the HERV-7q family, with motifs of exogenous origin or induced exogenously would be

capable of triggering or worsening a pathological process or on the contrary of promoting protection or partial remission or a complete and permanent cure.

5 The detection made possible of the HERV-7q type domains suggests possible applications at the prophylactic, prognostic and diagnostic level; for example, immunological approaches or gene amplification, which make it possible to compare normal individuals serving as reference with patients, would
10 be capable of promoting screening, of improving early detection of the outbreak of the disease and/or of monitoring the progression of a pathological condition in patients which may exhibit a susceptibility or in whom there has been an outbreak of the disease or in
15 individuals considered to be normal, based on current clinical criteria.

The specific nucleic and immunological probes, as defined, in the present invention are capable of promoting the identification and detection of motifs
20 which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune pathological conditions, at the forefront of which is multiple sclerosis.

25 The subject of the present invention is also hybrid nucleic sequences, characterized in that they comprise sequences or motifs belonging to the HERV-7q family, or of elements induced by motifs belonging to the HERV-7q family, with motifs of exogenous origin or
30 induced exogenously (exogenous retroviral sequences); such hybrid sequences are probably capable of triggering or worsening a pathological process or on the contrary of promoting protection or partial remission or a complete and permanent cure.

35 The subject of the present invention is also a diagnostic reagent for the differential detection of complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that

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it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate marker as well as of sequences as defined in Figures 18-21.

The sequences of the nucleic, ribonucleic and oligonucleotide probes used will be chosen from the env and gag regions or their flanking regions; for example the oligonucleotide primers for HERV-7q will be chosen from the regions situated between nucleotides 3065 and 4390, nucleotides 6965 and 9550 or nucleotides 2502-2865 of SEQ ID NO: 3, as well as from any adjacent sequence (upstream or downstream) capable of allowing specific amplification (Figure 1).

Among the appropriate markers, there may be mentioned radioactive isotopes, enzymes, fluorochromes, chemical markers (biotin), haptens (digoxigenin) and antibodies or appropriate base analogues.

Preferably:

- said reagent is selected from the sequences SEQ ID NO: 37-57 and is capable of being used as a primer,

- said reagent is selected from the following sequences:

a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),

a fragment of 2529 nt amplified by the pair of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R),

a fragment of 182 nucleotides, repeated twice, situated upstream of the gag domain at positions 2502-2611/2613-2865,

5 fragments encoding or not encoding all or part of enverin, comprising at least 14 nucleotides and in particular the fragments encoding the C-terminal portion of enverin, either from amino acid 291, or from amino acid 321, starting from the first methionine, and is capable of being used as a probe.

10 The subject of the present invention is also a method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the env or env and gag type, their normal or pathological variants, by hybridization and/or gene amplification, 15 carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analysed is brought into contact with at least one probe as defined above, and

20 (b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

In accordance with said method, it may comprise:

25 * prior to step (a):

. a step of preparing the relevant biological tissue or fluid,

. a step of extracting the nucleic acid to be detected, and

30 . at least one gene amplification cycle, and

* subsequent to step (b):

. a step of comparing the nucleic sequences obtained in said biological sample with the human endogenous retroviral sequences according to the 35 invention by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a deletion or a single mutation between the various sequences compared.

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In accordance with the invention, the human endogenous retroviral sequences according to the invention are thus compared with the nucleic sequences present in the biological sample to be analysed and
5 allow the detection of homologous sequences from patients suffering from pathological conditions likely to involve a modification of their genome.

Advantageously, said gene comparisons are carried out using genomic DNA obtained from control
10 individuals and from patients.

A conventional gene amplification by PCR will be carried out with the aid of 5'-sense and 3'-antisense primers delimiting or comprising the zone to be studied (env zone or gag zone).

Also advantageously, the sequences of the nucleic, ribonucleic and oligonucleotide probes used are chosen from the env and gag regions or their flanking regions; for example the oligonucleotides which are primers for HERV-7q will be chosen from the
15 regions situated between nucleotides 3065 and 4390 and nucleotides 6965 and 9550, and from any adjacent sequence (upstream or downstream) capable of allowing specific amplification (Figure 1), as specified above. They are preferably selected from the group consisting
20 of

a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),

a fragment of 2529 nt amplified by the pair
30 of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R).

The gene amplification step is in particular carried out with the aid of one of the following gene amplification techniques: amplification using
35 Q β -replicase, PCR, LCR, ERA, CPR or SDA.

The subject of the present invention is also chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence as defined above combined with an endogenous

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retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides, as defined above.

The subject of the present invention is also a method of detecting transcripts as defined above,
5 characterized in that it comprises:

- collecting messenger RNAs obtained from control biological samples (biological tissues, cells or fluids) and from a similar sample collected from patients, and
- 10 - the qualitative and/or quantitative analysis of said mRNAs by *in situ* hybridization, by dot-blot, Northern blotting, RNase mapping or RT-PCR, with the aid of a diagnostic reagent as defined above.

The subject of the present invention is also a
15 method for the detection and/or evaluation of an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, characterized in
20 that it comprises:

- depositing on an appropriate support, such as for example a nylon filter, a glass slide or their equivalent, cDNA or its equivalent obtained from clones, PCR products obtained from genomic DNA, RT-PCR
25 products obtained from transcripts or from specific oligonucleotide sequences, said DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, as defined above, consisting of transcripts
30 and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said
35 HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family and in

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which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as defined above,

- the hybridization of said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and
- the detection of the hybrids formed.

According to an advantageous embodiment of said method, said transcript or cDNA is selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

According to another advantageous embodiment of said method, said support comprises, in addition, any endogenous or exogenous retroviral sequence.

The method of DNA chips (Bowtell, (1999), Nature Genet., 21, 25-32), is used to evaluate the modification of the expression of all or part of some of the sequences of retroviral origin of the HERV-7q type and flanking sequences. Briefly, DNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or specific oligonucleotide sequences are deposited on a support, such as for example a nylon filter, a glass slide or their equivalent. The deposited nucleic sequences cover the various retroviral domains described above, as well as the contiguous sequences and the flanking genes. In order to detect possible alternative splicing processes, specific DNAs are synthesized per step of 500-600 nucleotides with an overlap of 250-300 nucleotides on either side. The alternative splicings already identified will be the subject of a specific synthesis. The hybridization is carried out with the

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aid of a probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, members of the various ethnic populations, patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, including multiple sclerosis. In this case, a μg fraction and up to a few μg of mRNA or up to a few μg or a few tens of μg of RNA, depending on the method used and the size of the DNA chip involved, are sufficient for the synthesis of the nucleic probe. The nucleic probe is suitably labeled so as to allow subsequent detection, such as for example by fluorescence or by an equivalent method.

The use of bi- or even multicolored probes makes it possible to specify the concerted expression of several genes in parallel, while taking advantage, furthermore, of a precise normalization. The results are acquired automatically, such as for example by a laser scanning system or its equivalent.

Two types of DNA chips are designed, on the one hand chips having an exhaustive set of sequences, and on the other hand specific DNA chips enabling targeting to a more specific application.

For example, a critical sequence in that it would contain a difference relating to a deletion or even a mutation is detected with the aid of specific oligonucleotides (Wang et al., (1998), Science, 280, 1077-1082). The polymorphism associated with a base or with a mutation is detected with the aid of four oligonucleotides possessing one of the four sequence possibilities at the level of a base (A, C, G or T); for each point difference, the 4 oligonucleotides are deposited and the hybridization intensities are compared. Furthermore, an alternative splicing is detected using DNAs corresponding to a single effective or putative exon; the gene is therefore analyzed exon by exon. The DNA chips also relate, by extension, to

any endogenous or exogenous retroviral sequence, such as for example ERV-9, ERV-K, ERV-L, ERV-H, ERV-4, ERV-6, ERV-8, ERV-10, ERV-15, ERV-16, ERV-17, ERV-18, ERV-21, ERV-24, ERV-33, ERV-34, ERV-36, ERV-40, ERV-42, 5 ERV-MLN, ERV-FRD, ERV-FTD and the like), as well as all the putative exon sequences (identified by the existence of sequence tags and corresponding transcripts) or effective exon sequences, and which are situated on either side up to a distance of 120 kb of 10 the endogenous retroviral sequences of the HERV-7q type.

The comparative study is carried out between a control sample and the sample to be tested, in a prophylactic, diagnostic or therapeutic perspective, 15 such as for example the early detection of a modification of the expression of one of the sequences, in a cell, a tissue or an organism, the identification of a sequence associated with a susceptibility or with any pathological condition, the monitoring of the 20 progression of the pathological condition or the monitoring of a treatment and the evaluation of its efficacy.

Apart from the applications already mentioned, the advantage of the method makes it possible, more 25 generally, to make an assessment of the changes observed in an individual, which constitutes to a certain extent an identity card, which facilitates an epidemiological approach which makes it possible to establish novel correlations between a particular 30 observed profile and a pathological condition, in the absence of an *a priori* regarding this pathological condition.

The subject of the present invention is also a kit for the detection and/or evaluation of an auto- 35 immune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in addition to the buffers necessary for carrying out the methods as defined above:

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- diagnostic reagents A as defined above, and
- reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/de-regulation or alteration is associated with the normal or pathological expression or with the regulation/de-regulation of motifs belonging to said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

According to an advantageous embodiment of said kit, said reagents B are selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, as well as the sequences represented in Figures 13-17, 22-26.

The subject of the present invention is also products of translation, characterized in that they are encoded by a nucleotide sequence as defined above.

The subject of the present invention is also a peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences SEQ ID NO: 1-22, 28 and 61, as defined above, according to the combinations offered by the use of the various possible reading frames (see also Figures 18-21).

Said peptide also includes the derived peptides or polypeptides comprising between 5 and 540 amino acids (SEQ ID NO: 23-36 and SEQ ID NO: 58 and their fragments of at least 5 amino acids) and in particular a fragment of 538 amino acids, starting at the first methionine of the sequence SEQ ID NO: 26 (enverin).

According to an advantageous embodiment of said peptides they are in particular selected from the

sequences SEQ ID NO: 23-36, 58, in particular the sequence SEQ ID NO: 26 and its C-terminal fragments, either from the amino acid 291, or from the amino acid 321, starting from the first methionine.

5 According to another advantageous embodiment of said peptides, they are obtained from nucleic sequences as defined above, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr
10 (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).

The invention thus includes the deduced peptides or the deduced proteins corresponding to all or part of the nucleic sequences described in the
15 invention, and optionally exhibiting modifications with the reference sequences described in the invention, when they are expressed in some patients. In particular, the invention includes the complete or partial sequences obtained according to the 3 sense
20 reading frames and the 3 reverse and complementary reading frames (see Figures 18-21).

Advantageously, the analysis of the structure of the env domain of HERV-7q, called enverin, made it possible to demonstrate successively:

25 - an N-terminal signal peptide (region 1-21) and two transmembrane domains (region 320-340; 455-477), responsible for interactions with membrane lipid or protein motifs,

- an immunomodulatory motif of the CKS-17
30 (Haraguchi et al., (1995), 92, 5568-5571)/CKS-25 type. It is possible to note, in this regard, the presence of an **RalD** motif inside the peptide of the CKS-17/CKS-25 type of HERV-7q and a motif **RvaD** at position 363 which correspond to the consensus W/RxxD, proposed for the
35 active site of the TGF- β s (Huang et al., J. Biol. Chem., 1997, 272, 27155-27159), potent factors associated with growth, with differentiation and with morphogenesis and which are associated with many human pathological conditions, such as tumor processes (Tang

et al., (1998), Nat. Med., 4, 802-807) or neuro-degenerative diseases (Flanders et al., (1998), Prog. Neurobiol., 54, 71-85). The peptides according to the invention containing these motifs can advantageously
5 serve as antagonists by inhibiting the attachment of the TGF- β s to their natural receptors,

- N-glycosylation motifs. The glycosylation of the envelope proteins of retroviruses appears to be directly associated with their functional properties,
10 for example by influencing the number of determinants available in the T cells or by promoting recognition of antigens by the T cells. Glycosylation could play a role in the outbreak or the spread of a pathological condition with an autoimmune component. The
15 glycosylations are necessary for maintaining the conformation of certain epitopes, in particular during the production of a recombinant envelope protein so as to develop a diagnostic reagent and to promote the efficacy of a possible vaccine. Positions 171, 210,
20 216, 236, 244, 283 and 411. Expected number at random: 3.2

- prenylation sites. Prenylation is an essential mechanism for attachment to the cell membrane and for the targeting of certain proteins. This
25 targeting process could be essential for the production of specific therapeutic agents capable of interfering with the production and regulation of the traffic of cellular complexes calling into play proteins involved in the cell interactions, growth and movement.
30 Positions 188 and 290. Expected number at random: 1.8

- targeting sites in the endoplasmic reticulum. These sites could make it possible to bring about the targeting toward the endoplasmic reticulum in order to carry out the modifications necessary for promoting
35 membrane crossing. Positions 353 and 431. Expected number at random: 0.2

Moreover, the inventors have shown that a number of peptides derived from the env protein of HERV-7q (enverin) have a high affinity/half-life for

the class I HLA alleles. CADD analysis has made it possible to select candidate peptides, for which the best scores are indicated in Table I:

5

TABLE I

Location	Sequence	HLA molecule	Score	Sequence No.
399	FLGEECCYYV	A-0201	7214	SEQ ID NO: 68
462	LLFGPCIFNL	A-0201	1792	SEQ ID NO: 69
189	CLPLNFRPYV	A-0201	1453	SEQ ID NO: 70
439	GLLSQWMPWI	A-0201	488	SEQ ID NO: 71
263	CLPSGIFV	A-0201	5103	SEQ ID NO: 72
444	WMPWILPFL	A-0201	897	SEQ ID NO: 73
252	IRWVTPPTQI	B-2705	3000	SEQ ID NO: 74
432	LRNTGPWGLL	B-2705	2000	SEQ ID NO: 75
158	LRTHTRLVSL	B-2705	2000	SEQ ID NO: 76
316	KRVPILPFVI	B-2705	1800	SEQ ID NO: 77
25	CRCMTSSSPY	B-2705	1000	SEQ ID NO: 78
137	TRVHGTSSPY	B-2705	1000	SEQ ID NO: 79
124	AREKHVKEVI	B-2705	600	SEQ ID NO: 80
478	SRIEAVKLQM	B-2705	600	SEQ ID NO: 81
442	SQWMPWILPF	B-2705	500	SEQ ID NO: 82
405	CYYVNQSGI	Kd	2400	SEQ ID NO: 83
346	FYYKLSQEL	Kd	2400	SEQ ID NO: 84
244	TYTTNSQCI	Kd	2400	SEQ ID NO: 85
291	SFLVPPMTI	Kd	1600	SEQ ID NO: 86
406	YYVNQSGIV	Kd	1200	SEQ ID NO: 87
167	LFNTTLTGL	Kd	1152	SEQ ID NO: 88
463	LFGPCIFNL	Kd	960	SEQ ID NO: 89
253	RWVTPPTQI	Kd	480	SEQ ID NO: 90
449	LPFLGPLAAI	B-5102	2200	SEQ ID NO: 91
3	LPYHIFLFTV	B-5102	1210	SEQ ID NO: 92
331	GALGTGIGGI	B-5102	798	SEQ ID NO: 93
321	LPFVIGAGVL	B-5102	550	SEQ ID NO: 94
499	RRPLDRPAS	B-2705	600	SEQ ID NO: 95
194	FRPYVSIPV	B-2705	600	SEQ ID NO: 96
383	RRALDLLTA	B-2705	600	SEQ ID NO: 97
39	WRMQRPNGI	B-2705	600	SEQ ID NO: 98
423	DRIQRAEEL	B14	1800	SEQ ID NO: 99
158	LRTHTRLVSL	B14	600	SEQ ID NO: 100
359	ERVADSLVTL	B14	540	SEQ ID NO: 101
463	LFGPCIFNLL	Kd	1658	SEQ ID NO: 102
345	QFYYKLSQEL	Kd	1152	SEQ ID NO: 103
443	QWMPWILPFL	Kd	691	SEQ ID NO: 104
405	CYYVNQSGIV	Kd	500	SEQ ID NO: 105
474	NFVSSRIEAV	Kd	480	SEQ ID NO: 106
221	GPLVSNLEI	B-5102	1320	SEQ ID NO: 107
190	LPLNFRPYV	B-5102	726	SEQ ID NO: 108
449	LPFLGPLAAI	B-5101	1144	SEQ ID NO: 109
488	EPKMQSKTKI	B-5101	968	SEQ ID NO: 110
3	LPYHIFLFTV	B-5101	629	SEQ ID NO: 111
125	REKHVKEVI	Kk	1000	SEQ ID NO: 112
312	KPRNKRVPIL	B7	800	SEQ ID NO: 113
378	VVLQNRAL	Db	792	SEQ ID NO: 114

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Location	Sequence	HLA molecule	Score	Sequence No.
377	AVVLQNRRL	Db	660	SEQ ID NO: 115
321	LPFVIGAGV	B-5101	629	SEQ ID NO: 116
304	DLYSYVISK	A3	540	SEQ ID NO: 117
301	TEQDLYSYVI	Kk	500	SEQ ID NO: 118

This Table I indicates an estimation of the dissociation half-life of a peptide of enverin with an allele of the class I HLA system (the tables of Parker coefficients: J. Immunol, (1994), 152, 163-175). The location indicates the position of the first amino acid of the peptides tested in the enverin sequence. The one-letter code is used for the amino acid sequence. The scores around 500 or greater than 500 were selected. By way of comparison, an analysis was carried out on a concatenation of peptides (polypeptide of 4968 amino acids) reputed to bind the molecules of the class I major histocompatibility complex (Rammensee, Immunogenetics, (1995), 41, 178-228); the ten best scores recorded for nonapeptides and the HLA type A_0201 are respectively 4984, 4047, 2406, 1267, 800, 705, 607, 591, 591 and 577.

It can be seen from this Table I that some molecules of the type I major histocompatibility complex are capable of binding peptides derived from enverin, thus assimilated with peptides of viral or tumor origin, at the level of the endoplasmic reticulum. The complexes formed at the level of the endoplasmic reticulum are then transported to the cell surface, which causes the destruction of the target cell by the cytotoxic T lymphocytes. The peptides identified generally comprise 8 to 10 amino acids. Studies have shown that some alleles of the class I HLA system are thus associated with certain pathologies, in particular with an autoimmune character, such as HLA-B27 with rheumatoid spondylitis or HLA-B51 with Behçet's disease.

A peptide capable of binding a particular class I molecule is consequently capable of functioning as a T cell epitope.

Consequently, the present invention also includes the fragments 399-471 and 244-271 of enverin which advantageously group together several epitopes having high affinity for various haplotypes of the class I HLA system. The use of all or some of these polypeptides is consequently capable of promoting an increase in the T cell repertoire, by allowing better efficacy of the immune response in the context of the various immunotherapeutic, prophylactic or vaccine strategies. These polypeptides may be advantageously delivered for example by the use of viral vectors, viral or synthetic particles, lipopeptides, conventional adjuvants, naked nucleic acids or nucleic acids adsorbed on particles, or liposomes.

For the purposes of the present invention, the peptides may be chemically or biochemically modified; some of the amino acids may be replaced with an analogous amino acid, according to conventional criteria for homologies (A or G; S or T; I, L or V; F, Y or W; N or Q; D or E).

The subject of the present invention is also immunogenic or vaccine compositions for protecting against autoimmune diseases, in particular in at-risk subjects, characterized in that it comprises at least one peptide comprising at least one motif of the CKS type and/or at least one peptide consisting of a motif having affinity with one of the haplotypes of the class I or class II HLA system and a pharmaceutically acceptable vehicle.

According to an advantageous embodiment of said composition, said motif is selected from the group consisting of peptides, as defined in Table I above.

According to another advantageous embodiment of said composition, said peptide has the following sequence:

sequence CKH: LQNRALDLLTAERGGTclFLGEECCYYV
(SEQ ID NO: 120).

It is remarkable to note at the level of position 380 of the enverin protein, the contiguity

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of the motifs of the CKS-17 type (underlined) and of the peptide having the highest score (in bold; see peptide at position 399 in Table I, SEQ ID NO: 68) in the sequence CKH.

5 The clonal activation of the subgroups of lymphocytes, for example of cytotoxic lymphocytes, by the peptides in Table I and by extension their homologues, is blocked by conventional immunotherapy means such as for example serotherapy and vaccination.

10 The combination of two sequences or of the sequences analogous to the CKH peptide (SEQ ID NO: 120), is capable of causing a synergistic process in the immune response, which could bring into play additional signaling and activation pathways
15 capable of modulating the lymphocyte activation.

 The vaccination relates to the production of antibodies directed against the peptides of Table I, according to the rules of the prior art and according to the methods of release controlled by artificial or
20 cellular implants using a composition as defined above and by using gene therapy means, such as for example expression of nucleic sequences encoding the peptides of Table I. Consequently, the subject of the invention is also immunogenic or vaccine compositions,
25 characterized in that they comprise a vector including at least one nucleic sequence encoding a peptide as defined in Table I, optionally combined with a sequence encoding a motif of the CKS-17 type.

 The serotherapy relates to the use of
30 neutralizing antibodies produced from the peptides of Table I and their homologues.

 The protein products generated by the endogenous retroviral sequences or produced in parallel may be advantageously characterized by micro-methods of
35 analysis and quantification of peptides and proteins: HPLC/FPLC or equivalent, capillary electrophoresis or equivalent, microsequencing techniques (Edman method or equivalent, mass spectrometry and the like).

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The subject of the invention is also antibodies directed against one or more of the peptides described above and their use either for carrying out a method, in particular a differential method, of *in vitro* detection of the presence of such a sequence in an individual, or for the preparation of a composition capable of being used in serotherapy in neuropathological conditions with an autoimmune component.

Said antibodies are advantageously polyclonal or monoclonal antibodies obtained by an immunological reaction from a human, mammalian or avian organism or other species toward the proteins, as defined above.

The subject of the present invention is a method for the differential immunological screening of normal or pathological human endogenous retroviral sequences of the HERV-7q family, characterized in that it comprises bringing a biological sample into contact with an antibody according to the invention, the reading of the result being visualized by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

By way of illustration, such an *in vitro* diagnostic method according to the invention comprises bringing a biological sample collected from a patient into contact with antibodies according to the invention and detecting with the aid of any appropriate method, in particular with the aid of labeled anti-immunoglobulins, the immunological complexes formed between the proteins produced normally or pathologically and the antibodies.

Monoclonal or polyclonal antibodies, produced from antigens corresponding to synthetic peptides, or recombinant polypeptide or proteins make it possible to monitor the expression of the peptides or proteins produced normally or pathologically. The analysis is preferably carried out by ELISA or equivalent, Western blotting or equivalent, or by immunohistochemistry.

The peptides or proteins, derived from the endogenous retroviral sequences or whose expression is associated with the expression of these endogenous retroviral sequences, are tested for and identified.

5 The subject of the present invention is also a method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological
10 conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences according to the
15 invention.

 The subject of the present invention is also the application of the nucleic sequences or of the protein sequences according to the invention to the diagnosis of, to the prognosis of, to the evaluation of
20 genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part
25 of the nucleic sequences according to the invention and related endogenous or exogenous forms are involved.

 The subject of the present invention is also hybrid nucleic sequences, characterized in that they comprise nucleic sequences or motifs according to the
30 invention, combined with sequences or motifs of endogenous origin or of exogenous origin or induced exogenously.

 The subject of the present invention is, in addition, a recombinant cloning or expression vector,
35 characterized in that it comprises a nucleic sequence in accordance with the invention.

 Therapeutic strategies may be envisaged by using some of the nucleic sequences contained in HERV-7q and the sequences of the same family or deduced

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polypeptide structures or by the use of peptides or proteins, or of specific antibodies.

In accordance with the invention, all or part of the endogenous retroviral nucleic sequences of the
5 HERV-7q type may be used for use as a vector or as vector elements for therapeutic use, in particular the LTR sequences and the gag region (SEQ ID NO: 2, 21 and 22).

The advantage of such sequences lies in the
10 safety of the vector thus formed, in the possibility of a targeted specific insertion in a well-defined region by a strategy similar to homologous recombination, in cellular targeting, which is optionally transient in the case of a placental expression in women. Another
15 aspect relates to the possibility of combining with the genes of interest the biologically active retroviral motifs (immunomodulatory peptides, as represented in the sequences SEQ ID NO: 68-118, below, fusogenic peptide and the like).

The subject of the present invention is also
20 transgenic animals, characterized in that they comprise all or part of a sequence of the HERV-7q type (SEQ ID NO: 1-22 and 61).

Table II below establishes the correspondences
25 between the sequence numbers as they appear in the sequence listing and the name of the various sequences.

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FOOTNOTES

- 40 -
TABLE II

SEQ ID NO:	DESIGNATION
1	Nucleic acid: 7 env
2	Nucleic acid: gag
3	Nucleic acid: HERV-7q
4	Nucleic acid: HE2
5	Nucleic acid: HE3
6	Nucleic acid: HG3
7	Nucleic acid: HE4
8	Nucleic acid: HE5
9	Nucleic acid: HE6
10	Nucleic acid: HG6
11	Nucleic acid: HE7
12	Nucleic acid: HE8
13	Nucleic acid: HG8
14	Nucleic acid: HE9
15	Nucleic acid: HE10
16	Nucleic acid: HE11
17	Nucleic acid: HG11
18	Nucleic acid: HE12
19	Nucleic acid: HG12
20	Nucleic acid: R1
21	Nucleic acid: R1F
22	Nucleic acid + deduced env protein: HERV-7q
23	Fragment of deduced env protein according to SEQ ID NO: 22
24	Fragment of deduced env protein according to SEQ ID NO: 22
25	Fragment of deduced env protein according to SEQ ID NO: 22
26	Protein: enverin
27	Fragment of deduced env protein according to SEQ ID NO: 22
28	Nucleic acid + protein deduced from gag: HERV-7q
29	Fragment of deduced gag protein according to SEQ ID NO: 28
30	Fragment of deduced gag protein according to SEQ ID NO: 28
31	Fragment of deduced gag protein according to SEQ ID NO: 28
32	Fragment of deduced gag protein according to SEQ ID NO: 28
33	Fragment of deduced gag protein according to SEQ ID NO: 28
34	Fragment of deduced gag protein according to SEQ ID NO: 28
35	env protein: reading frame 1
36	gag protein
37	Nucleic acid: G1F (primer)
38	Nucleic acid: G1R (primer)
39	Nucleic acid: G2F (primer)
40	Nucleic acid: G2R (primer)
41	Nucleic acid: G4F (primer)
42	Nucleic acid: G3F (primer)
43	Nucleic acid: G4R (primer)
44	Nucleic acid: G5R (primer)
45	Nucleic acid: E1F (primer)
46	Nucleic acid: E1R (primer)
47	Nucleic acid: E2F (primer)
48	Nucleic acid: E2R (primer)
49	Nucleic acid: E3F (primer)
50	Nucleic acid: E3R (primer)
51	Nucleic acid: E4F (primer)

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SEQ ID NO:	DESIGNATION
52	Nucleic acid: E4R (primer)
53	Nucleic acid: E5F (primer)
54	Nucleic acid: E6F (primer)
55	Nucleic acid: E5R (primer)
56	Nucleic acid: ExF (primer)
57	Nucleic acid: ExR (primer)
58	Protein gag
59	Nucleic acid: Sequence A (insertion sequence)
60	Nucleic acid: Sequence B (insertion sequence)
61	Nucleic acid: HE13
62	Nucleic acid: RH7
63	Nucleic acid: RAM75
64	Nucleic acid: RAV73
65	Nucleic acid: RBP3
66	Nucleic acid: HI3
67	Nucleic acid: LTX
68	Peptide Table I
69	Peptide Table I
70	Peptide Table I
71	Peptide Table I
72	Peptide Table I
73	Peptide Table I
74	Peptide Table I
75	Peptide Table I
76	Peptide Table I
77	Peptide Table I
78	Peptide Table I
79	Peptide Table I
80	Peptide Table I
81	Peptide Table I
82	Peptide Table I
83	Peptide Table I
84	Peptide Table I
85	Peptide Table I
86	Peptide Table I
87	Peptide Table I
88	Peptide Table I
89	Peptide Table I
90	Peptide Table I
91	Peptide Table I
92	Peptide Table I
93	Peptide Table I
94	Peptide Table I
95	Peptide Table I
96	Peptide Table I
97	Peptide Table I
98	Peptide Table I
99	Peptide Table I
100	Peptide Table I
101	Peptide Table I
102	Peptide Table I
103	Peptide Table I
104	Peptide Table I
105	Peptide Table I

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SEQ ID NO:	DESIGNATION
106	Peptide Table I
107	Peptide Table I
108	Peptide Table I
109	Peptide Table I
110	Peptide Table I
111	Peptide Table I
112	Peptide Table I
113	Peptide Table I
114	Peptide Table I
115	Peptide Table I
116	Peptide Table I
117	Peptide Table I
118	Peptide Table I
119	Nucleic acid: BLIMP-1
120	Peptide: CKH
121	Nucleic acid: F645 (primer)
122	Nucleic acid: PSSD (primer)

In addition to the preceding arrangements, the invention also comprises other arrangements which will emerge from the description which follows, which refers to exemplary embodiments of the method which is the subject of the present invention as well as to the appended drawings, in which:

- Figure 1. Human nucleic sequence HERV-7q, whose analysis and treatment make it possible to characterize a novel endogenous retroviral structure. The repeat nucleic regions of type R1 and R2 and the *gag*, *pol* and *env* domains are underlined. The *gag* and *env* type domains are in italics. The region homologous to a noncoding 3' portion of Rab7 is double underlined.

- Figure 2. Map of the human endogenous retroviral region HERV-7q. The upper part of the figure corresponds to an anonymous region of the human genome situated on the long arm of chromosome 7. The repeat domains (1), *gag* (2), *pol* (3) and *env* (4) of HERV-7q can be identified. The C-terminal *env* region (4.3) is prolonged upstream in the form of a long open reading frame (4.2). The domain 4.1 corresponds to the N-terminal region of the *env* domain.

- Figure 3. Comparison of the repeat nucleic sequences situated at the boundaries of HERV-7q. The 5'

(top) and 3' (bottom) repeat nucleic regions are compared and the identical bases are indicated by two dots.

5 - Figure 4. Deduced sequence having an open reading frame in the env-type domain of HERV-7q according to the longest open reading frame rule.

10 - Figure 5. Sequences around the CKS-17 domain identified in various deduced env domains of the HERV-7q family and comparison with reference CKS-17 motifs.

1) HE2 - 2) HERV-7q - 3) GenBank accession No.: M85205 - 4) HE7 - 5) HE9 - 6) CKS-17; the peptide motif endowed with immunomodulatory properties is underlined - 7) gp20 of retrovirus type D (SRV-Pc).

15 - Figure 6. Possible deduced sequence of the gag-type domain identified in HERV-7q established according to the longest open reading frame rule. X and / correspond to a non-sense codon and to a reading frame shift, respectively. The underlined sequence
20 corresponds to the beginning of the pol domain.

- Figure 7. Comparison of the nucleic regions covering the gag region of HERV-7q (top) and HERV-TcR (bottom) and their flanking regions. The identical bases are specified by two dots.

25 - Figure 8. Example of nucleic alignments of the env-type domain of HERV-7q with similar env-type domains present in human endogenous retroviral sequences of the same family. The non-sense codons are underlined: 1) HERV-7q - 2) HE2 03) HE3 - 04) HE4.

30 - Figure 9. Nucleic alignments between the gag domain of HERV-7q and the corresponding domains belonging to the same family. Comparison with fragments of gag domains isolated from infectious retroviral agents. Sequences of infectious retroviral origin: EMBL
35 database accession No.: 1) A60168 - 2) A60201 - 3) A60200 - 4) A60171. Human endogenous retroviral sequences: 5) HERV-7q - 6) HG11 - 7) HG3. The figures indicated in the endogenous sequences correspond to the number of nucleotides inserted in order to optimize the

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alignment with the gag-type sequences identified in retroviruses of infectious origin.

5 - Figure 10. Alignment of a deduced gag protein motif (top) belonging to an infectious retrovirus (EMBL accession No.: A60200) with the deduced gag protein motif (bottom) identified in HERV-7q. The non-sense codons are in bold and underlined. The identical amino acids are specified by 2 dashes. One dash indicates a deletion or a homologous amino acid.

10 - Figure 11. Alignment of an env motif (top) belonging to an infectious retrovirus (EMBL accession No.: A60170) with the env motif (bottom) identified in HERV-7q. The homologous nucleotides are specified by two dots and the deletions by a dash.

15 - Figure 12. Comparison between the env domain of HERV-7q (top) and the env domain of HERV-9 (bottom). The 66% homology is limited to the 3' region of the env domain of HERV-7q and HERV-9, respectively between nucleotides 8976 nt and 9500 nt of HERV-7q and
20 nucleotides 2898 nt and 3465 nt of HERV-9 (GenBank accession No.: X57147). Numerous insertions/deletions are also observed.

25 - Figure 13. Homology between a portion of the sequence of the transcript encoding RH7 (top, SEQ ID NO: 62) and an RGH2 motif (bottom - GenBank accession No.: D11018).

30 - Figure 14. Identification of the sequence of the transcript encoding RAM75 (SEQ ID NO: 63), corresponding to the gene for an ATPase of PEX1 type. The coding exons are underlined. The initiation and non-sense codons as well as the putative polyadenylation sites are in bold and underlined. The region in italics corresponds to the beginning of the endogenous retroviral sequence RH7.

35 - Figure 15. Sequence of the transcript encoding RAV73 (SEQ ID NO: 64), situated at 0.7 kb downstream of HERV-7q; the nucleic sequences capable of encoding one or more polypeptides are underlined.

- Figure 16. Comparison between the 3' LTR sequence (top) of HERV-7q and the intron sequence LTX (SEQ ID NO: 67), situated in the FMR2 gene, associated with fragile X (bottom).

5 - Figure 17. Detection of modifications on the nucleotide sequence (ID NO: 3), in patients suffering from MS. The modified bases, in at least one patient, are underlined. The primers used are in italics (sequences SEQ ID NO: 121 and 122). The initiation ATG and the non-sense codon are in bold.

10 - Figure 18. The env coding portion of the HERV-7q sequence (sequence ID NO: 3), with 3 reading frames.

15 - Figures 19, 20, 21. Separate presentation of the env protein according to the 3 reading frames.

20 - Figure 22. Nucleic sequence containing the retroviral sequence RH7 situated in 5' of the HERV-7q sequence. The sequence in italics corresponds to the beginning of the HERV-7q sequence. The RH7 sequence is underlined. Two putative polyadenylation sites are in bold.

25 - Figure 23. Sequence of the transcript encoding RBP3 containing nucleotide motifs identified in the nucleic sequence encoding the Blimp-1 gene.

30 - Figure 24. Sequence of the transcript encoding APS.

 - Figure 25. Sequence of the transcript encoding Blimp-1; the coding portion is underlined; the initiation and termination codons are in bold.

 - Figure 26. Sequence of the transcript encoding FMR2. The coding portion is underlined. The initiation and non-sense codons are in bold.

 It should be clearly understood, however, that these examples are given solely by way of illustration of the subject of the invention and do not in any manner constitute a limitation thereto.

EXAMPLE 1: Detection, by gene amplification, of a nucleic sequence belonging to a domain of the gag or env type according to the invention, in a genomic DNA sample of human or mammalian origin

5 The gene amplification is carried out using genomic DNA isolated from blood. An anticoagulant treatment is carried out with 1 ml of a citrate solution (per liter: 4.8 g of citric acid, 13.2 g of sodium citrate, 14.7 g of glucose) per 6 ml of fresh
10 blood. After centrifugation of 20 ml of blood for 15 min at 130 000 g, the supernatant is removed and the fraction enriched with white blood cells is transferred into a new tube and then recentrifuged under the same conditions as above. The fraction enriched with white
15 blood cells is resuspended in an extraction buffer (10 mM Tris-HCl, 0.1 M EDTA, 20 µg/ml of pancreatic RNase treated so as to eliminate the DNases, 0.5% SDS, pH 8.0), and then incubated for 1 hour at 37°C. Proteinase K is added at a final concentration of
20 100 µg/ml. The suspension of lysed cells is incubated at 50°C for 3 hours, with occasional stirring, and then treated with an equal volume of phenol equilibrated with 0.5 M Tris-HCl, pH 8.0. The emulsion formed is placed on a wheel for one hour and then centrifuged at
25 5 000 g for 15 min at room temperature. The aqueous solution is treated and deproteinized by a triple phenol extraction in order to obtain a level of purification corresponding to an absorbance A260/A280 final ratio greater than 1.75. The aqueous fraction is
30 precipitated with 0.2 vol. of 10 M sodium acetate and 2 vol. of ethanol. The DNA is then either collected with the tip of a bent Pasteur pipette, or centrifuged at 5 000 g for 5 min at room temperature. The DNA or the DNA pellet is washed twice with 70% ethanol and
35 then taken up in 1 ml of TE, pH 8.0 so as to be eluted, with gentle stirring, for 12 to 24 hours.

Oligonucleotides specific for the endogenous sequences described according to the invention are chosen in order to amplify the gag or env region of the

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endogenous retroviral regions described according to the invention. The genomic DNA studied is obtained from patients having pathological conditions such as multiple sclerosis and from individuals reputed to be healthy.

The thermostable DNA polymerases used were chosen for their high accuracy during the amplification process, such as Vent DNA polymerase (Biolabs) and the like, and are used according to the conditions recommended by the supplier.

The amplification strategy uses, depending on the case, a simple PCR, or a nested or seminested PCR.

Oligonucleotides used to amplify the gag region:

- primer G1F, sense, located in the region upstream of the gag domain of HERV-7q (SEQ ID NO: 37),
- primer G1R, antisense, located in the 3' terminal region of the gag domain (SEQ ID NO: 38).

The fragment of 1505 nt amplified by the pair G1F-G1R; 1505 nt is used to generate the probes capable of hybridizing the various PCR amplification products.

- primer G2F, sense nested (SEQ ID NO: 39),
- primer G2R, antisense nested (SEQ ID NO: 40),
- primer G4F, sense nested (SEQ ID NO: 41),
- primer G3F, sense nested (SEQ ID NO: 42),
- primer G4R, antisense nested (SEQ ID NO: 43),
- primer G5R, antisense nested (SEQ ID NO: 44).

Oligonucleotides used to amplify the env region of HERV-7q:

- primer E1F, sense (SEQ ID NO: 45),
- primer E1R, antisense (SEQ ID NO: 46).

The fragment of 2529 nt amplified by the pair of primers E1F-E1R is used to generate the probes capable of hybridizing the various PCR amplification products.

- primer E2F, sense (SEQ ID NO: 47),
- primer E2R, antisense (SEQ ID NO: 48),
- primer E3F, sense (SEQ ID NO: 49),
- primer E3R, antisense (SEQ ID NO: 50),

- primer E4F, sense (SEQ ID NO: 51),
- primer E4R, antisense (SEQ ID NO: 52),
- primer E5F, sense (SEQ ID NO: 53),
- primer E6F, sense (SEQ ID NO: 54),
- 5 - primer E5R (SEQ ID NO: 55),
- primer ExF (SEQ ID NO: 56),
- primer ExR (SEQ ID NO: 57).

The PCR is carried out using 50 to 200 ng of genomic DNA. The PCR conditions are those recommended
10 by the supplier. The amplification cycle conditions are carried out in 50 μ l: denaturation of 94°C for 1 min, hybridization of 70°C for 1 min, and extension at 72°C for 1 to 2 min, depending on the amplified fragments. After 35 cycles, a terminal reaction is carried out at
15 72°C for 10 min. Automated sequencing of the amplified samples is carried out with the aid of an Applied Biosystems type ABI 377 sequencer or another comparable model, according to the protocols provided by the manufacturer.

20 In the case of a nested or seminested PCR, the same experimental conditions are used, the only difference being that the genomic DNA sequence is replaced with 5 to 10 μ l of the amplification product derived from the first PCR.

25 Two independent amplifications are carried out using the same sample. A control reaction is carried out by replacing the DNA sample with water in order to detect possible contaminants.

EXAMPLE 2: Detection, by gene amplification, of a
30 nucleic sequence according to the invention in a biological sample of genomic DNA collected from patients having an existing candidate pathological condition or suspected of having this pathological condition

35 The amplification protocol is the same as in Example 1, apart from the origin of the sample which is obtained from patients having a candidate pathological condition. A genomic DNA sample reputed to be normal is

systematically integrated into the set of amplified pathological samples and then analyzed.

5 The PCR products are separated on a 1.5% agarose gel and then transferred in the presence of 0.4 N sodium hydroxide on a charged nylon membrane. Hybridization is carried out with a specific probe corresponding to the PCR fragments amplified either with the pair G1F-G1R or the pair E1F-E1R. The probe is labeled by incorporating dUTP-digoxigenin according to the supplier's protocol (Boehringer Mannheim). The hybridization is carried out in a hybridization buffer (5XSSC, 50% formamide, 0.1% lauroylsarcosine, 0.02% SDS, 2% blocking reagent Boehringer) overnight at 42°C. The Southern is washed for twice 5 min at room temperature in a 2XSSC solution containing 0.1% SDS. Next, a high stringency wash is carried out twice for 15 min at 55°C in a 0.1XSSC solution containing 0.1% SDS. The hybridization is visualized according to the supplier's protocol (Boehringer Mannheim), in the presence of a chemiluminescent substrate for alkaline phosphatase, of the CSPD or CDP-STAR type. The filter is visualized after a 15 min exposure at 60°C.

SSCP (*single strand conformation polymorphism*) analysis makes it possible to detect discrete modifications of the sequence of the fragments amplified by PCR. The PCR is carried out in the presence of dCTP labeled with ³²P. The sample to be analyzed is denatured at 95°C for 10 min in the presence of loading buffer, and then immediately loaded onto a 10% polyacrylamide gel containing 7.5% glycerol. The migration is carried out at 4°C at 8-10 W. The gel is dried and then autoradiographed.

The PCR fragments likely to exhibit an alteration of their nucleotide sequence are sequenced according to Example 1.

Hybridization with the aid of a specific oligonucleotide (17 mers to 20 mers) corresponding to the modified nucleotide region makes it possible to identify the samples having an identical modification

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(ASO method). Briefly, the southern is hybridized with an oligonucleotide which is distally labeled either with ^{32}P , or in the presence of digoxigenin (according to the Boehringer Mannheim protocol) and then washed under stringent conditions at 65°C in a 6XSSC solution containing 0.05% sodium pyrophosphate.

For example, an automated nucleotide sequencing was carried out on six PCR fragments obtained from 5 patients suffering from MS and a control reputed to be normal, and which were amplified using the primers F645: CTTCAAACAACAACCAGGAGG (SEQ ID NO: 121) (situated 26 nucleotides upstream of the initiation methionine of enverin) and PS5D: TTGGGGAGGTTGGCCGACGA (SEQ ID NO: 122) (situated 6 nucleotides downstream of the non-sense codon of enverin). Modifications of the sequence of enverin were observed on the DNA from some patients (Figure 17).

EXAMPLE 3: Detection of a protein according to the invention in a biological sample

- Preparation of a purified protein fraction of cerebrospinal fluid from patients suffering from MS

After a treatment at 56°C for 30 min and removal of the immunoglobulins on a G HiTrap protein column (Pharmacia), the equivalent of 10 ml of CSF is deposited on a DEAE Sepharose CL-6B column (Pharmacia). The elution is carried out in 20 mM Tris-HCl, pH 8.8, and a gradient from 0 to 0.4 M NaCl, and then the fraction is dialyzed twice against a phosphate-NaCl buffer (PBS). After concentration on Ultrafree-MC (Millipore), the fraction is deposited on a Superose 12 column (FPLC Pharmacia) and eluted in the presence of PBS. After separation by polyacrylamide-SDS gel electrophoresis and electrotransfer onto an Immobilon-P membrane (Millipore), the protein bands are subjected to controlled trypsin hydrolysis.

- Analysis of the protein fraction by mass spectrometry

The peptides digested in the presence of trypsin are analyzed by the MALDI-TOF method, which

allows the analysis of peptides present in a mixture (COTTRELL J.S., Pept. Res., 1997, 7, 115-124). The peptides characterized according to their mass are compared with the proteins and with the associated proteins according to the invention.

EXAMPLE 4: Detection of specific antibodies to the env domain of HERV-7q

The identification of a long open reading frame in the env sequence of HERV-7q made it possible to determine a deduced protein sequence SEQ ID NO: 22 and 35 and Figures 18-20 of a region of the said gene.

The protein sequences deduced from the sequences ID NO: 22, 35 and Figures 18-20 are positioned as follows with respect to Figure 1 or the sequence ID NO: 3:

SEQ ID NO: 22 (reading frame 1) and Figure 19: beginning of the coding sequence: position 7874, end of the coding sequence 1st nonsense codon (position 9493)

SEQ ID NO: 35: beginning of the coding sequence: position 7874, end of the coding sequence 1st nonsense codon (position 9493) (reading frame 1)

Figure 19: beginning of the coding sequence: position 6970, end of the coding sequence 1st nonsense codon (position 9493) (reading frame 1)

Figure 20: beginning of the coding sequence: position 6971, the end of the reading frame is shifted depending on the case by 1, 2 or 3 codons

Figure 21: beginning of the coding sequence: position 6972, the end of the reading frame is shifted depending on the case by 1, 2 or 3 codons

Various peptides corresponding to all or part of SEQ ID NO: 22 (see SEQ ID NO: 23-27 and 35) were synthesized by genetic engineering in order to test their antigenic specificity toward sera or tissues from patients suffering from MS, for example. Briefly, all or part of the env region of HERV-7q is subcloned into the vectors pQE30, 31 and 32. The vectors pQE30, 31 and 32 contain, in 5' of the multiple cloning site, the consensus sequences for transcription (the strong T5

bacteriophage promoter, 2 operators of the lactose operon) and translation (one synthetic ribosome binding site). Likewise, pQE30, 31 and 32 possess, in 3', the phage 1 transcription terminator as well as a Stop
5 codon for translation. The expression of the protein is carried out after transformation in *E. coli* M15. The plasmid pQE30, 31 and 32 possess, upstream of the multiple cloning site, the coding sequence for a succession of 6 histidines having affinity for nickel
10 ions. This stretch allows the purification of the expressed chimeric protein by adsorption on a resin consisting of a chelating ligand, nitrotriactic acid (NTA), charged with 4 nickel ions (NI-NTA resin, Qiagen).

15 The transformation is carried out by electroporation or treatment with calcium chloride. For example, an *E. coli* M15 colony is incubated in 100 ml of LB medium containing 250 μ g of kanamycin, with stirring at 37°C until an OD⁶⁰⁰ of 0.5 is obtained.
20 After centrifugation for 5 minutes at 2000 g at 4°C, the bacterial pellet is taken up in 30 ml of TFB1 solution (100 mM rubidium chloride, 50 mM manganese chloride, 30 mM potassium acetate, 10 mM CaCl₂, 15% glycerol, pH 5.8), at 4°C for 90 minutes. After a
25 centrifugation of 5 minutes at 2000 g at 4°C, the bacterial pellet is taken up in 4 ml of TFB2 solution (10 mM rubidium chloride, 10 mM MOPS, 75 mM CaCl₂, 15% glycerol, pH 8). The cells may be kept at -70°C in aliquots of 500 μ l. 20 μ l of the ligation and 125 μ l of
30 competent cells are mixed and placed on ice for 20 minutes. After a heat shock of 42°C for 90 seconds, the cells are stirred for 90 minutes at 37°C in 500 ml of Psi-broth medium (LB medium supplemented with 4 mM MgSO₄, 10 mM potassium chloride). The transformed cells
35 are plated on LB-agar dishes supplemented with 25 μ g/ml of kanamycin and 100 μ g/ml of ampicillin, and the dishes are incubated overnight at 37°C.

The potentially recombinant clones are subcultured in an orderly manner on a nylon filter

deposited on an LB-agar dish supplemented with 25 μ g/ml of kanamycin and 100 μ g/ml of ampicillin. After one night at 37°C, the recombinant clones are located by hybridization of the plasmid DNA with the nucleotide probe amplified by PCR with the pair of primers according to SEQ ID NO: 45 and SEQ ID NO: 46.

An independent colony containing the insert is inoculated at 20 ml of LB medium supplemented with 25 μ g/ml of kanamycin and 100 μ g/ml of ampicillin. After one night at 37°C, with stirring, 500 ml of the same medium are incubated at 1/50 with this preculture until an OD⁶⁰⁰ of 0.8 is obtained, and then 1 to 2 mM final of IPTG is added. After 5 hours, the cells are centrifuged for 20 minutes at 4 000 g.

A portion of the cellular pellet is taken up in 5 ml of sonification buffer (50 mM of sodium phosphate, pH 7.8, 300 mM NaCl) and then placed on ice. After rapid sonification, the cells are centrifuged for 20 minutes at 10 000 g. A portion of the cellular pellet is taken up in 10 ml of a 30 mM Tris/HCl-20% sucrose solution pH 8. The cells are incubated for 5 to 10 minutes, with stirring, after addition of 1 mM EDTA. After a centrifugation of 10 minutes at 8 000 g at 4°C, the pellet is taken up in 10 ml of 5 mM ice cold MgSO₄. After 10 minutes on the ice, with stirring, the cells are centrifuged for 10 minutes at 8 000 g at 4°C.

The pellet is taken up in 5 ml/g in buffer A (6 M GuHCl (guanidine hydrochloride), 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 8), 1 hour at room temperature. The lysate is centrifuged for 15 minutes at 10 000 g at 4°C, and the supernatant is supplemented with 8 ml of Ni-NTA resin, pre-equilibrated in buffer A. After 45 minutes at room temperature, the resin is poured into a column, washed with 10 times the column volume with buffer A and then with 5 times the column volume with buffer B (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 8). The column is washed with buffer C (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 6.3) until A280 is less than 0.01. The

recombinant protein is eluted with 10 to 20 ml of buffer D (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 5.9) and then with 10 to 20 ml of buffer E (8 M urea, 0.1 M sodium phosphate, 0.01 M Tris/HCl, pH 4.5), and then with 20 ml of buffer F (6 M HCl, 0.2 M acetic acid). After SDS-PAGE analysis, the purified fraction(s) containing the chimeric protein allowed the production of antibodies in rabbits. The antibodies obtained are tested by Western blotting after visualization with a secondary antibody coupled to alkaline phosphatase.

Antibodies are obtained in the same manner, using peptides synthesized chemically according to the Merrifield technique (G. Barany and B. Merrifield, 1980, in *The peptides*, 2, 1-284, E. Gross and J. Meienhofer, Academic Press, New York).

The specific antibodies obtained are used for detection of the serum or tissue expression of all or part of the endogenous retroviral sequences according to the invention, in normal and pathological cases.

The proteins of serum or tissue origin are separated on acrylamide-SDS gel and then transferred onto a nitrocellulose filter with the aid of a Novablot 2117-2250 apparatus (LKB). The transfer is carried out on a Hybond C-extra sheet (Amersham) using a 100 mM CAPS buffer pH 11, methanol, water (V/V/V: 1/1/8) containing 1 mM CaCl_2 . After a transfer of 1 hour at 0.8 mA/cm², the sheet is saturated for 1 hour at room temperature in PBS-0.5% gelatin. The sheet is brought into contact with the specific antibody at the concentration of 1/1 000 in PBS-0.25% gelatin. After 2 hours, the filter is washed 3 times 15 minutes in PBS-0.1% Tween-20, and then the filter is incubated for 30 minutes in the presence of a secondary antibody coupled to alkaline phosphatase (Promega), diluted 1/7 500 in PBS-0.25% gelatin. After three washes in PBS-0.1% Tween-20, the filter is equilibrated in a buffer (100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM MgCl_2). The visualization is carried out in the presence

of 45 μ l of NBT at 75 mg/ml and 35 μ l of BCIP at 50 mg/ml, per 10 ml of alkaline phosphatase buffer.

The chimeric proteins obtained by genetic engineering are also used for tests of biological activity, such as for example the test for biological activity of the CKS-17-type peptide identified in the env domain of HERV-7q (Figure 5).

EXAMPLE 5: Production of ribonucleic probes encoding the env sequences of HERV-7q

The PCR fragments obtained are subcloned into the plasmid PGEM 4Z (Promega) which possesses on either side of its multiple cloning site, promoter sequences for the SP6 and T7 RNA polymerases.

The method of competence used is electroporation. The plasmid and the PCR fragment are hybridized in a ratio of 50 ng of vector (SmaI cleavage) to 100 ng of PCR fragment (made blunt ended by treatment with the Klenow fragment of DNA polymerase). The incubation takes place overnight at 22°C in ligation buffer (66 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 1 mM dithioerythritol, 1 mM ATP) in the presence of 1 u of T4 DNA ligase and is then stopped by denaturation for 10 minutes at 65°C. In parallel, the *E. coli* JM 105 strain is inoculated overnight at 37°C in LB medium. This preculture is diluted 1/500 and placed at 37°C until an OD⁶⁰⁰ equal to 1 is obtained. For the remainder of the procedure, the cells will always be stored at cold temperature. After centrifugation for 5 minutes at 3 500 g at 4°C, the cellular pellet is resuspended in 1/4 vol. of ultra-pure ice-cold water. This step is repeated 5 to 6 times. The pellet is then resuspended in 1/4 000 vol. of water; 10% of sterile glycerol is added, allowing preservation of the electrocompetent cells, in aliquots of 10 μ l at 20°C. 1 μ l of the ligation is added to 50 μ l of electrocompetent cells; the mixture is subjected to an electrical discharge of 12.5 kV/cm, applied for 5.8 ms. The cells are rapidly resuspended in the SOC medium, incubated for 1 hour at 37°C and

then plated in the presence of 2% X-Gal in dimethylformamide, and 10 mM IPTG, on an LB-agar dish supplemented with ampicillin (100 µg/ml). After one night at 37°C, the potentially recombinant white clones are subcultured in an orderly manner on an LB/ampicillin dish and in parallel on a nylon filter deposited on an LB/ampicillin dish. These two dishes are incubated overnight at 37°C. The recombinant clones are then located by hybridization with a nucleic probe amplified by PCR with the pair of primers according to SEQ ID NO: 45 and SEQ ID NO: 46 and labeled with digoxigenin.

The recombinant clones are cultured in 50 ml of LB/ampicillin medium (100 µg/ml), with stirring, overnight at 37°C. After centrifugation at 3 500 g for 15 minutes at 4°C, the bacterial pellet is taken up in 4 ml of P1 buffer (50 mM Tris-HCl, 10 mM EDTA, 400 µg/ml RNase A, pH 8) and 4 ml of P2 buffer (200 mM NaOH, 1% SDS). The medium is incubated at room temperature for 5 minutes. After addition of 4 ml of P3 buffer (2.55 M potassium acetate, pH 4.8), the mixture is centrifuged at 12 000 g for 30 minutes at 4°C. This supernatant is applied to a Qiagen type 100 column, pre-equilibrated with 2 ml of QBT buffer (750 mM NaCl, 50 mM MOPS, 15% ethanol, pH 7), the column is washed with twice 4 ml of QC buffer (1 M NaCl, 50 mM MOPS, 15% ethanol, pH 7) and the DNA is eluted with 2 ml of QF buffer (1.2 M NaCl, 50 mM MPOS, 15% ethanol, pH 8). The DNA is precipitated with 0.8 vol. of isopropanol and centrifuged at 12 000 g at 4°C for 30 minutes. The pellet is washed with 70% ice-cold ethanol and then the plasmid DNA is taken up in twice 150 µl of TE buffer.

The ribonucleic probes are used as specific probes, in particular for the detection of the transcripts expressed by the endogenous retroviral sequences according to the invention.

EXAMPLE 6: Construction of a transgenic mouse containing all or part of the gene for enverin

A transgenic mouse containing all or part of the HERV-7q sequence (SEQ ID NO: 3) is constructed so as to identify the sequences responsible for the tissue specificity, and to evaluate the role of all or part of the endogenous retroviral motifs of the HERV-7q type, in particular all or part of the peptide motifs of enverin. The microinjection technique used refers to the conventional technique (Hogan et al., (1994), Manipulating the mouse embryo, Cold Spring Harbor, Cold Spring Harbor Laboratory Press) or to its equivalents. Forms identical to the normal human molecule of motifs of the HERV-7q type, including enverin, or forms which are mutated, deleted, having insertions, or truncated are tested in order to determine the motifs which are critical both from the normal and pathological point of view, and more particularly during fetal development and during tumor processes.

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As is evident from the above, the invention is not at all limited to its embodiments, implementations and applications which have just been described more explicitly; it embraces on the contrary all the variants which may occur to a specialist in this field, without departing from the framework or scope of the present invention.

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CLAIMS

1. A purified nucleic acid fragment, characterized
5 in that it comprises all or part of a sequence encoding
a human endogenous retroviral sequence, which has at
least env-type retroviral motifs, corresponding to the
sequence SEQ ID NO: 1 or to a sequence exhibiting a
10 level of homology with the said sequence SEQ ID NO: 1
greater than or equal to 80% on more than 190
nucleotides or greater than or equal to 70% on more
than 600 nucleotides for the env-type domains.
2. The nucleic acid fragment as claimed in
claim 1, characterized in that it has retroviral motifs
15 corresponding to an env domain and corresponding to the
sequence SEQ ID NO: 1 and retroviral motifs
corresponding to a gag domain and corresponding to the
sequence SEQ ID NO: 2 or to a sequence exhibiting a
level of homology greater than or equal to 80% on more
20 than 190 nucleotides or greater than or equal to 70% on
more than 600 nucleotides for the env-type domains and
a level of homology greater than or equal to 90% on
more than 700 nucleotides or greater than or equal to
70% on more than 1 200 nucleotides for the gag-type
25 domains, the said motifs having no insertion or
deletion of more than 200 nucleotides.
3. A nucleic acid fragment, characterized in that
it comprises a segment of a sequence as claimed in
claim 1 or claim 2 and in particular the sequence
30 SEQ ID NO: 3-22, 28 and 61, the complementary nucleic
sequences and the reverse sequences complementary to
the preceding sequences as well as fragments derived
from the coding regions of the preceding sequences
corresponding to a shifting frame greater than or equal
35 to 14 nucleotides or their complementary sequences.
4. Transcripts, characterized in that they are
generated from the sequences as claimed in any one of
claims 1 to 3.

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5. A diagnostic reagent for the differential detection of complete or partial human endogenous nucleic sequences, having retroviral motifs, selected from the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2, characterized in that it is selected from the group consisting of the sequences SEQ ID NO: 1-22, 28, 37-57, 59-61 and 121-122, the complementary nucleic sequences and the reverse sequences complementary to the preceding sequences, of nucleotide fragments capable of defining or of identifying the sequences SEQ ID NO: 1 and/or SEQ ID NO: 2 and any flanking sequence or any sequence overlapping them as well as of fragments derived from the coding regions of the sequences SEQ ID NO: 1-22 and 61, corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences, optionally labeled with an appropriate label.

6. The reagent as claimed in claim 5, characterized in that it is chosen from the regions situated between nucleotides 3065 and 4390, nucleotides 6965 and 9550 or nucleotides 2502-2865 of SEQ ID NO: 3.

7. The reagent as claimed in claim 5, characterized in that it is selected from the sequences SEQ ID NO: 37-57, 59-60 and 121-122 and in that it is capable of being used as a primer.

8. The reagent as claimed in claim 5, characterized in that it is selected from the following sequences:

- a fragment of 1505 nt amplified by the pair of primers SEQ ID NO: 37 and SEQ ID NO: 38 (primers G1F and G1R),

- a fragment of 2529 nt amplified by the pair of primers SEQ ID NO: 45 and SEQ ID NO: 46 (primers E1F and E1R),

- a fragment of 182 nucleotides, repeated twice, situated upstream of the gag domain at positions 2502-2611/2613-2865,

and in that it is capable of being used as a probe.

9. The reagent as claimed in claim 5, characterized in that it is chosen from the group consisting of the fragments encoding or not encoding all or part of enverin, in particular the fragments comprising at least 14 nucleotides and more particularly the fragments encoding the C-terminal portion of enverin, either from the amino acid 291, or from the amino acid 321, starting from the codon encoding the first methionine.

10. A method for the rapid and differential detection of the endogenous retroviral nucleic sequences of the env or env and gag type, their normal or pathological variants, by hybridization and/or gene amplification, carried out using a biological sample, which method is characterized in that it comprises:

(a) a step in which a biological sample to be analyzed is brought into contact with at least one probe as claimed in claim 5, claim 6 or claim 8, and

(b) a step in which the product(s) resulting from the nucleotide sequence-probe interaction is detected by any appropriate means.

11. The method of detection as claimed in claim 10, characterized in that it comprises:

* prior to step (a):

. a step of preparing the relevant biological tissue or fluid,

. a step of extracting the nucleic acid to be detected, and

. at least one gene amplification cycle carried out with the aid of at least one reagent as claimed in any one of claims 5 to 7, and

* subsequent to step (b):

. a step of comparing the nucleic sequences obtained in the said biological sample with the human endogenous retroviral sequences as claimed in any one of claims 1 to 3, by any appropriate means and in particular by sequencing, Southern blotting, restriction cleavage, SSCP or any other method which makes it possible to identify an insertion or a

deletion or a single mutation between the various sequences compared.

12. A method of detecting the transcripts as claimed in claim 4, characterized in that it comprises:

5 - collecting messenger RNAs obtained from control biological samples and from a similar sample collected from patients, and

- the qualitative and/or quantitative analysis of the said mRNAs by *in situ* hybridization, by dot-blot, Northern blotting, RNase mapping or RT-PCR, with
10 the aid of a diagnostic reagent as claimed in any one of claims 5 to 9.

13. Chimeric sequences, characterized in that they consist of a fragment of 17 to 40 nucleotides of a flanking sequence selected from the group consisting of
15 transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to said
20 HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in
25 which one of the ends cannot be at a distance exceeding 120 kb, associated with an endogenous retroviral motif of the HERV-7q type comprising between 17 and 40 nucleotides as claimed in claims 1 to 4.

14. A method for the detection and/or evaluation of
30 an overexpression/underexpression or of a modification of at least one of the endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or of their associated flanking sequences, as claimed in any one of claims 1 to 9, characterized in that it
35 comprises:

- depositing on an appropriate support, cDNA obtained from clones, PCR products obtained from genomic DNA, RT-PCR products obtained from transcripts or from specific oligonucleotide sequences, the said

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DNA sequences being endogenous retroviral sequences or fragments of sequences of the HERV-7q type and/or their flanking sequences, consisting of transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/deregulation or alteration is associated with the normal or pathological expression or with the regulation/deregulation of motifs belonging to the said HERV-7q family, these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of the said HERV-7q family and in which one of the ends cannot be at a distance exceeding 120 kb, and/or a chimeric sequence as claimed in claim 13,

- the hybridization of the said support with at least one appropriately labeled probe obtained, for example, by retrotransposition of an RNA mixture obtained from biological cells, tissues or fluids obtained from controls reputed to be normal, from members of various ethnic populations, from patients suffering from pathological conditions often associated with expression of retroviruses, such as tumor processes, or such as autoimmune diseases, and

- the detection of the hybrids formed.

15. The method as claimed in claim 14, characterized in that the said transcript or cDNA is selected from the group consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

16. The method as claimed in claim 14 or claim 15, characterized in that the said support comprises, in addition, any endogenous or exogenous retroviral sequence.

17. The kit for the detection and/or evaluation of an autoimmune disease and in particular of neuropathological conditions with an autoimmune etiology, characterized in that it comprises, in

addition to the buffers necessary for carrying out a method according to any one of claims 14 to 16:

- diagnostic reagents A as claimed in any one of claims 5 to 9, and

5 - reagents B consisting of the transcripts and cDNAs of the genomic sequences, which encode all or part of a factor, whose function, regulation/de-regulation or alteration is associated with the normal or pathological expression or with the regulation/de-regulation of motifs belonging to said HERV-7q family,
10 these sequences corresponding to nucleotide sequences encoding genes situated in flanking regions situated upstream and/or downstream of a retroviral sequence of said HERV-7q family, of which one of the ends cannot be
15 at a distance exceeding 120 kb,

- which reagents are preferably attached to an appropriate support.

18. The kit as claimed in claim 17, characterized in that said reagents B are selected from the group
20 consisting of the sequences SEQ ID NO: 62-67 and 119 and their fragments corresponding to a shifting frame greater than or equal to 14 nucleotides or their complementary sequences.

19. Translational products, characterized in that they
25 are encoded by a nucleotide sequence as claimed in any one of claims 1 to 4.

20. A peptide, characterized in that it is capable of being expressed with the aid of a nucleotide sequence selected from the group consisting of the sequences
30 SEQ ID NO: 1-22, 28 and 61 as claimed in any one of claims 1 to 4.

21. The peptide as claimed in claim 20, characterized in that it includes the derived peptides comprising between 5 and 540 amino acids and in particular a
35 fragment of 538 amino acids, starting at the first methionine of the sequence SEQ ID NO: 26 (enverin).

22. The peptide as claimed in claim 20 or claim 21, characterized in that it is selected from the group consisting of:

- . the sequences SEQ ID NO: 23-36;
 - . the sequence SEQ ID NO: 58;
 - . a C-terminal fragment of the sequence SEQ ID NO: 26, either from the amino acid 291, or from the amino acid 321, starting from the first methionine of the sequence SEQ ID NO: 26;
 - . a peptide of the CKS-17/CKS-25 type present in one of the sequences SEQ ID NO: 23-36 or 58; and
 - . the peptides having affinity with one of the haplotypes of the class I or class II HLA system and in particular the fragments 399-471, 244-271 of enverin, as well as the peptides having the sequence SEQ ID NO: 68-118, in accordance with Table I.
23. The peptide as claimed in any one of claims 20 to 22, characterized in that it is obtained from nucleic sequences as claimed in any one of claims 1 to 4, in which at least one non-sense codon may be replaced with a codon encoding one of the following amino acids: Phe (F), Leu (L), Ser (S), Tyr (Y), Cys (C), Trp (W), Gln (Q), Arg (R), Lys (K), Glu (E) or Gly (G).
24. Immunogenic or vaccine compositions for protecting against autoimmune diseases, in particular in at motif selected risk subjects, characterized in that it comprises at least one peptide comprising at least one motif of the CKS type and/or at least one motif selected from the group consisting of the peptides having affinity with one of the haplotypes of the class I or class II HLA system and at least one pharmaceutically acceptable vehicle.
25. The composition as claimed in claim 24, characterized in that said peptide having affinity with one of the haplotypes of the class I or class II HLA system is selected from the group consisting of the peptides as defined in Table I.
26. The composition as claimed in claim 24 or claim 25, characterized in that said peptide has the sequence SEQ ID NO: 120.

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27. An antibody, characterized in that it is directed against one or more of the peptides as claimed in any one of claims 20 to 23.

28. A pharmaceutical composition, characterized in that it comprises neutralizing antibodies produced from the peptides of Table I (SEQ ID NO: 68-118) and their homologues.

29. A method for the differential immunological screening of normal or pathological human endogenous retroviral sequences of the HERV-7q family, characterized in that it comprises bringing a biological sample into contact with an antibody as claimed in claim 27, the reading of the result being visualized by an appropriate means, in particular EIA, ELISA, RIA, fluorescence.

30. A method for the identification and detection of endogenous retroviral motifs which are abnormally expressed in the context of pathological conditions associated with cancer, or of neuropathological conditions, in particular autoimmune neuropathological conditions, at the forefront of which is multiple sclerosis, characterized in that it comprises the comparative analysis of the sequences extracted from a biological sample and the sequences as claimed in any one of claims 19 to 23.

31. An application of the sequences as claimed in any one of claims 1 to 9, 13, 14 or 19 to 23 to the diagnosis of, to the prognosis of, to the evaluation of genetic susceptibility to, any induced, congenital or acquired human diseases, in particular those with cancerous, autoimmune and/or neurological components, such as multiple sclerosis, the associated syndromes and the neurodegenerative diseases in which all or part of the sequences as claimed in to any one of claims 1 to 5 and related endogenous or exogenous forms are involved.

32. Hybrid nucleic sequences, characterized in that they comprise sequences or motifs as claimed in any one of claims 1 to 9, combined with sequences or motifs of

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endogenous origin or of exogenous origin or induced exogenously.

33. A recombinant cloning or expression vector, characterized in that it comprises a nucleic sequence
5 as claimed in any one of claims 1 to 4.

34. An immunogenic or vaccine composition, characterized in that it comprises a vector including at least one nucleic sequence encoding a peptide as defined in Table I, optionally combined with a sequence
10 encoding a motif of the CKS-17 type.

35. A gene therapy vector, characterized in that it comprises all or part of the endogenous retroviral nucleic sequences of the HERV-7q type as claimed in any one of claims 1 to 4.

15 36. The vector as claimed in claim 35, characterized in that said sequences are selected from the group consisting of the sequences SEQ ID NO: 2, 20 and 21.

37. Transgenic animals, characterized in that they comprise all or part of a sequence of the HERV-7q type
20 (SEQ ID NO: 1-22, 28 and 61).

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Abstract

The invention concerns a novel nucleic sequence and deduced protein sequence family with whole or partial human endogenous retroviral motifs. The invention also concerns the detection and/or the use of said nucleic sequences and said corresponding protein sequences or fragments of said sequences, for diagnostic, prophylactic and therapeutic uses, in particular for neuropathological conditions with autoimmune constituent such as multiple sclerosis. Said purified nucleic acid sequences comprise all or part of a sequence coding for a human endogenous retroviral sequence having at least *env*-type retroviral motifs, corresponding to the sequence SEQ ID NO:1 or to a sequence having a homology level with said sequence SEQ ID NO:1 not less than 80% of more than 190 nucleotides or not less than 70% on more than 600 nucleotides for *env*-type domains. The invention further concerns the use of the flanking or adjacent sequence of said sequences and controlled by the latter, as diagnostic reagents.

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CCCTGGGGCCGGCTTCCTTTCTGGGATGAGGGCAAAACGGCTGGAGATACAGCAATTATCTTGGCACTGAG
 AGACAGGACTAGCTGGATTTCCTAGGCCGACTAAGAAATCCCTAAGCCTAGCTGGGAAGGTGACCACGTCCAC
 CTTTAAACACGGGGCTTGAACCTTAGCTCAGACCTGACCAATCAGAGAGCTCAGTAAATGCTAATTAGGGA
 AAGACAGGAGGTAAAGAAATAGGCAATCATCTATTGGCTGAGAGCAGCAGGAGGGGACAAATCGGGATA
 TAAACCCAGGCAATCGAGCTGGCAACAGCAGCCGCCCTTTGGGTCTCTTCCCTTTGGTATGGGAGCTTTTC
 ATGCTATTTCACTCTATTAAATCTTGAACCTGCACTCTTCTGGTCCATGTTTCTTACGGCTCGAGCTGAGCT
 TTTGCTCACCCTGCCACCACTGCTGTTTGGCAACAGCCGAGAGCTGCGCTGACTCCCATCTCTTGGATCT
 GCAGGGTGTCCGCTGTGCTGCTGATCCAGCGAGGGGCCCATTTGCCGCTCCCAATTGGGCTAAAGGCTTGCA
 TTGTTCTCTGACGGCTAAGTGGCTGGGTTTGTCTAATTGAGGTGAACACTAGTCACTGGGTTCATGGTTC
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 CCGTGAGGCCAAGAACTCCAGGTGAGAGAATACGAGGCTTGCCACCATCTTGGAAAGCGGCTGCTACCATCT
 TGGAAAGTGGTTCAACCACTCTTTGGGAGCTCTGTGAGCAAGGACCCCGGTAAACATTTGGCAACACGAA
 CGGACATCCAAAGTGGTGAATATATTGGACCACTTTCACCTTGTCTATTCTGTCTCTATCCCTTCTTAGAATTG
 GAGGAAATACCGGGCACTTGTGGCCAGTTAAACAGATTAGTGTGGCCACCGGACTTAAGACTCAGGTGT
 GAGGCTATCTGGGGAAAGGGCTTTCTAAACACCCCAACCTTCTGGGTGGGGACTTGGTTTGGCTCAAGCC
 AGCTTCCACTTTCAGTTTCTTGGGAAAGCCGAGGGCCGACTAGAGGCAGAAAGCTGTCTCTGAACTCC
 GGCAGTAGCCGGTGTAGATCATGGTGTAGCCAGAACTCTCAACAGTCCGCCATGCATGCCACCCCTATCTTTC
 CTCTGACCCATACCTCTGGTCCCAACCACTTCTTCAAAGTGTAGCCCAAAATCTCTTACCTC
 TGAATATACTTCTCTGATCCCTGCTCTAGTACTATTGGTTCAGACTTCCATTTCTCTAGCAAGTGT
 ATCTCCAAAGGATCTAAGGAAGCTCTGCGCTGCTCTTAGGCACCTAGGCTATAACCCAGGGAGTCTTAT
 CCCTGGTGTCTCTCCCAATTTAGGCATACAGCTCTTGACATGGGCAGTTATGTAGGACCCACTCCCTACCCAC
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 GAAAGAGAGAGAGACAGAGAGGAGAGAGAGACAGTGAAGAGACAGAGAGAGAGAGACAAAGAGGAGAG
 AGAGAGAGTCAAGAGAGAGAAAGAGAGAAAGAGAAATAGTAAAAAACAGTGTGCCCTATCTCTTAAAAAGCC
 GGGTAAATTTAAACCTGTACTTGTATTAATGAAGGTCTTCTCTGACCCCTATAGCACTCCCAATCCACTTTG
 TGGTCAGTGTAAATAGAGCATAGGCCGAAAGCACTGAGGCCATTGACACCCGTAAGCTTCCCTATCAAAAA
 TCCTTAACCCAGTAAAGGAGATAGGCCGAAAGCACTGAGGCCATTGACACCCGTAAGCTTCCCTATCAAAAA
 AAGTAACTTTTAGAGGAAACCTCATTGTGAGCACACCTCACCTGTTGAGAATTATTCTAATAAAAAAGCA
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 ACCACTGATAATTCCCTTAACCCAGCAGATTTCCTAACGGGATTAAATCTTAATTACCAATACAAAGGTCCG
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 TTAGCAGCCCTGGAAGGAACTCACCCCTGAGCAGCAAAAGGCAATGTTGGGCAAGCTGGTAAAGGACCACTAG
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 AAGGAGATAGACAAAGGGTAAACAGTGAACCAAGAGTGCATATATCCCAATTAAGACCCCTCCAGG
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 AACAGACTTAGGTAAATTTCTAGATAACCCCTGATGGGTATATTGATGTTTACAAAGGTTAGGACAAATTCT
 TGATCTGACATGGAGAGATATAATGTCACTGTCTAAATCAGACACTAACCCCAATGAGAGAAAGTCCACCA
 AACTGCAAGCTGAGAGTTTGGGATCTCTGGTATCTCAGTCAGGTCAATGATAGGATGCAACAGAGGAAAG
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 GGCATTGAGGAAGCGTGCCTCTCTGTCACCTGACTCTTCTGAAGGCCAACTAATCTTAAAGCGTAAGTTTAT
 CACTCAGTCAGCTGCAGACATTAGAAAAAACTTCAAAGTCTGCGTAGGCGCCGAGGCAAACTTAGAAAC
 CCTATTGAAGTTGGCAACCTCGGTTTTTATAATAGAGATCAGGAGGAGCAGGCGGAACAGGACAAACGGGA
 TTAAGAAAAAGGCGACCGCTTTAGTCATGACCTCAGGCAAGTGGACTTTGGAGGCTCTGGAAGGGAAG
 GCTGGGCAAAATGAAATGCTAATAGGGCTTGTTCCTGCTGCGGTCTACAAGGACACTTTAAAAAGATTGTC
 CAAGTAGAAGTAAGCGCGCCCTCTGCTCATGCGCTTATTTCAGGGAATCACTGGAAGGCGCACTGCCCA
 GGGGACAAAGGTCCTCTGAGTCAGAAAGCACTAACAGATGATCCAGCAGGAGGACTGAGGGTGGCTGGGG
 AAGCGGCATCCCATGCCATCACCCCTCACAGAGCCCTGGGTATGCTTGCACCAATTGAGGCGGAGGAGTGTCT
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 CTGAGGGGCTCTAAGACGGGCACTACTAGATCTTCTCCAGCCACTAAGTTATGACTGGGGAGCTTTAT
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 CAGGGGCCATTATACACTGAACATAGGAGAAGGAACACCCGTTTGTGTCCCTGCTTGAAGGAAGTAA
 ATCTGAAAGTCTGGGCAACAGAGGAGCAATATGGACGAGCAAGAAATGCCGCTCTGTTCAAGTTAACTAA
 AGGATTCCACCTCTTTCTCTACCAAGGAGTACCCCTCAGACCCAAAGGCGCAACAGGACTCCAAAGG
 TTGTTAAGGACCTAAAGCCCCAAGGCTTAGTAAACCAATGCAGTAACCCCTGCAGTACTCCAATTTTAGGAG
 TACAGAAACCCAGACAGAGTGGAGGTTAGTGCAGACTCTCAGGATTATCAATGAGGCTGTGTTCTCTAT
 AGCCAGCTGTACTAGCCCTTATCTCTGCTTTCCCAATACAGAGGAAGGAGAGTGGTTTACAGTCTGGS
 ACCTTCAGGATGCTTCTCTGCTATCCCTGTACATCCTGACTCTCAATCTTGTGCTTGAAGTACTT

repeat
region

81

tandem
repeat
regionscag
domain201
domain

FIGURE 1.1

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CAAACCCCAACATCTCAACTCACCTGGACTATTTTACCCCAAGGGTTTCAGGGATAGTCCCATCTATTGGCC
 AGGCATTAGCCCAAGACTTTCAGGCAATCCTCATACCTGGACACTTGTCTTCCGGTAGGTGGATGATTACTT
 TTGGCCGCCCATTCAGAAACCTTTGTCCCATCAAGCCACCCAGCGCTCTCAATTTCCGTGCTACCTGTGG
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 CCCTCAGTGGGCACTAGATAATAGGAGAAGAAAAAGGGCAATATATATACAGACTCTAATATGCTTACC
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 CCGAGTACTCAGCAGGAGAAACAGAAATGGGGAACTCAGCAGGACAGTTTCTCCCTTCCGGGACGGCTAGCC
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 TTCAGTATCTACTAGTGTGGGTAGATACTTTCAGGGTTGGGAGAGGGCTTCCCTGTAGGACAGAAAAGG
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 ACAATAGCCCTGCTTTCCAGGCCACAGTAACCCAGGAGTATCCAGGGCTTAGGTATACGATATCACTTAC
 ACTGGCCTGAAGGCCACAGTCTTCAGGGAAGGTGAGAGAAATGAATGAAGCACTCAAGGACATCTAAAAA
 AGCAAAACCCAGGAAACCCACCTCAGATGGCTGCTGTGTGCTATAGCTTAAAAAGAACTCTGCACTTTC
 CCCAAAAAGCAGGACTTAGCCCATACGAAATGCTGTATGGAAGGGCTTCATAACCAATGACCTTGTGCTTG
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 AGGAGGAAAGTAACTAAATCAATAATCCCATGCCCCCTCCCTTATCATATTTTCTCTTACTGTCTCTT
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 ATGGAGAAATGCAAGCTTCCCGGAAATATTGATGCCCATCGTATAGGAGTCTTCTAAGGGAACCCCAAGCT
 CACTGCCACACCCATATGCCCGGCAACTGCTATCACTCTGCCACTCTTTGCAATGCAATGCAAACTACTCTA
 TTGGACAGGAAATATGATTAATCTTGTGCTTGGAGGACTTGGAGTCACTGTCTTGGACTTACTTCACT
 CCAAACTGGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAAGAGAAAAACATGTAAGAAAGTAATCTC
 CCAACTCACCCCGGTAGATGGCACTCTAGCCCTTACAAAGGACTAGATCTCTCAAACTACATGAACCCCT
 CCGTACCCATCTCTGCTTGGTAAAGCTATTTAAATACCACCTCACTGGGCTCCATGAGGTCTCGGCCCCAAA
 CCGTACTAATCTTGGATATGCCCTCCCTGAACTTCAGGCAATATGTTTCAATCCCTGTACCTGAAACATG
 GAACAACTTCAGGACAGAAAAATAACACCACTTCCGTTTATAGGAGCTCTTGTTTCAATCTGGAATTAAC
 CCACTACCTCAAACTCAGCTGTGTAATTTAGCAATAGTACATACACAACCACTCCCAATGCAATCAGGTG
 GGTAACTCTTCCACACAAATAGTCTGCCCTACCTCAGGAATATTTTGTCTGTGGTACCTCAGGCTATCG
 TTGTTGAATGGCTCTTCAATCTATGTGCTTCTCTCATTTCTAGTGGCCCTATGACCATCTACACTGA
 ACAGATTTATACAGTTATGTCATCTTACCCCGCAACAAAGAGTACCACTTCTTCTTCTTGTATAGG
 AGCAGGAGTCTAGGTGCACTAGGTACTGGCATTTGGCGGTATGACAGCTCTACTCAGTCTACTACAACT
 ATCTCAAGAACTAAATGGGGAGATGGAACCGGTCCCGGACTCGCTGGTCACTTGGCAAGATCAACTTAACT
 CCTAGCAGCAGTATGCTCTTCAAAATCGAAGAGCTTTAGACTTGGTAACCGCTGAAAGAGGGGAACCTGTT
 ATTTTAGGGGAAGATGCTGTTATTAATGTAATCAATCGGGAATGCTGACTGAGAAAGTTAAAGAAATTCG
 AGATCGAATCAACCTAGAGCAGAGGAGCTTCGAAGCACTGGAACCTTGGGGCTTCTCAGGCAATGGATGCC
 CTGGATTTCTCCCTTCTTAGGACCTCTAGGAGCTATAATATTGCTACTCTCTTTGGACCCCTGTATCTTAA
 CCTCCTTGTTAAGTTTGTGCTTTCAGAAATGGAAGCTGTAAAACTACAAATGGAGCCCAAGATGCACTGCA
 GACTAAGATCTACCGCAGACCCCTGGACCGGCTGCTAGCCCAAGATCTGATGTTAATGACATCAAAAGGCAC
 CCCTCCTGAGGAAATCTCAGCTGCACACCTCTACTACGCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCT
 TCGGCAACCTCTCCCAACAGCACTTAGGTTTTCCTGTTGAGATGGGGGACTGAGAGACAGGACTAGCTGGAT
 TTCCTAGGCTGACTAAGAAATCCCTAAGCCTAGCTGGGAAGGTGACCACATCCACCTTTAAACACGGGGCTTG
 CAACTTAGCTCACACCTGACCAATCAGAGAGCTCACTAAATGCTAATTAGGCAAGACAGGAGGTAAGAA
 ATAGCCAATCATCTATTGCTGAGAGCAGCAGGAGGAGCAATGATCGGGATATAAACCAAGTCTTCGAG
 CCGGCAACGGCAACCCCTTTGGGTCCCTCCCTTGTATGGGAGCTCTGTTTTCATGCTATTTCAGTCTAT
 TAAATCTTGAACCTGCACTCTTCTGCTCCATGTTTCTTACGGCTTGAAGTCTGCTCTGCTGCTATCCACC
 ACTGCTGTTTGGCCGCCACCGCAGACCCGCGCTGACTCCCATCCCTCTGGATCATGCAAGGTTCTCCGTGTG
 CTCTGATTCAGGAGGCAACCCATTCGCCCTCCCAATCGGGCTTAAAGGCTTGGCATTGTTCTGCTGATGGCTA
 AGTGCTGGGTTTCTCTAATTGAGCTGAACACTAGTCACTGGGTTCCATGGTTCTTCTGTGACCCACAG
 CTTCTAATAGAGCTATAACACTACCCGATGGCCCAAGGTTCCATTCTTGAATCCATAAGGCCAAGAACCC
 CAGGTCAGAGAACACGAGGCTTGGCACCATTCTGGAGCTCTGTGAGCAAGGACCCCAAGTAACACAACCA
 TGAGGGTGCAATGCAATGGGCCCAATATGGTAGAGCAAGGAAAGGAGGAGGAGGAGGAGGAGGAGGAGGAG
 AGTGAGCTGAATGCTGCTGCTGATGCTTCTGCTAGGTTTCTGCTGCTGAGCAGATTAACCCCTT
 GTTCACTTCTCAAGTAGGGCTTCTATTACAGCCCAATCAATCCCAACCCAGATGACAT

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FIGURE 1.2

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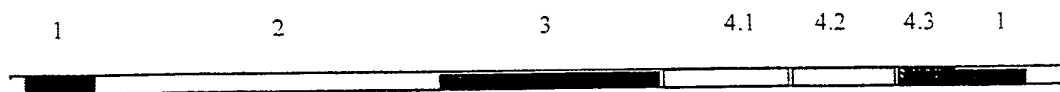


FIGURE 2

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FIGURE 3

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2
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IPMALPYHIFLFTVLLPSFTLTAPPPCRMTSSSPYQEFLLWRMQRPGNIDAPSYRSLSKG
 TPTFTAHTHMERNYHSATLCMHANTHYWTGKMINPSCPGGLGVTVCWYFTQTGMSDGG
 GVQDQAREKHVKEVISQLTRVHGTSSPYKGLDLSKLHETLRTHRLVSLFNTTLTGLHEV
 SAQNPTNCWICLPLNFRPYVSI PVPEQWNNFSTEINTTSVLVGPLVSNLEITHTSNLTCV
 KFSNTTYTNSQCIRWVTPTQIVCLPSGIFVCGTSAYRCLNGSSSESMCFLSFLVPPMT
 IYTEQDLYSYVISKPRNKRVPILPFVIGAGVLGALGTGIGGITTSTQFYKLSQELNGDM
ERVADSLVTLQDQLNSLAAVVLQNRRLDLLTAERGGTCLFLGEECCYYVNQSGIVTEKVKEIRDRIQORRAEELR
NTGPWGILLSQWMPWILPFLGPLAAIILLLLFGPCIFENLLVNFVSSRIEAVKLQMEPKMQSKTKIYRRPLDRPAS
RSDVNDIKGTPPEEISAAQPLLRPNASAGSS

FIGURE 4

- 1) NSLAAVVLQNRRLDLLTAESGGTFLFLEEK
- 2) NSLAAVVLQNRRLDLLTAERGGTCLFLGEEC
- 3) DSLAAVTLQNHQGLDLLTAEGGGLCYFLGEDC
- 4) DSLAAVTLQNHQGLDLLIAEGGGLCTFLGEEC
- 5) DSLAAVTLQNCRGLDLLTAEGGHHYTFLEEEC
- 6) LQNRRLDLLFLKEGGLC
- 7) DSLAKVVLQNRRLDLLTAEQGGICLALQEK

FIGURE 5

TSFVEKANGVKCHKYKLSFHXETTHNYVKSIVIYALQEAFRVYLPILPASPTPSPTNKDPPSTQMVQKEIDKRVNSEPKS
 ANIPQLXPLQAVGGREFGPARVHVPPSLPDLKQIKTDLGKFSNPDGYIDVLQGLGQFFDLTWRDIMSLLNQTLTPNER
 SATITAAXEFGDLWYLSQVNDRTTEEREXFPTGQAVPSLDPHWDTESEHGDWCCRHLCTVLEGLRKRTRKSMNYSM
 MSTITQGREENPTAFLERLREALRKASLSPDSSEGQILKRFITQSAADIRKKLQKSAVGPEQNLETLLNLATSVFY
 NRDQEEQAEQDKRDXKKGHRFSDHPQASGLWRLWKREKLKLNAXXGLLPVRSTRTLXKRLSKXXAAPSMPPLISRES
 LEGPLPQGTKVLXVRSHXPD/SSRT

FIGURE 6

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CCTGGCACTCCTGAGGGAAGTATAAATTATAACACCATCTTACAGCTAGACCTCTTTGTAGAAAAGGCA
CCTGGC-CTCCTGAGGGAAGTATAAATTATAACACCATCTTACAGCTAGACCTCTTTGTAGAAAAGAG
-CAATGGAGTGAAGTGCCATAAGTACAACTTTCTTTTCATTAAAGAGACAACCTACAATTATGTAAAAA
GCAATGGAGTGAAGTGCCATATGTACAACTTTCTTTTCATTAAAGAGATAACTCCCAATTATGTAAAAA
GTGTGATTTATGCCCTACAGGAAGCCTTCAGAGTCTACCTCCCTATCCCAGCAT--CCCCGACTCCTTCC
GTGTGATTTATGCCCTACAGGAAGCCTTCAGAGTCTACCTCCCGACCCAGCAGACCCCAACTCCTTCT
CCAATAATAAGGACCCCTTCAACCCCAATGGTCCAAAAGGAGATAGACAAAAGGGTAAACAGTGAAC
CCAATAATAAGGACCCCTTCAACCCCAATGGTCCAAAAGGAGATAGACAAAAGGGTAAACAGTGAAC
CAAAGAGTGCCCAATTATGCCCAATTATGACCC-CTCCAAGCAGTGGGAGGAAGAGAATTTCGGCCAGCCA
CAAAGAGTGCCCAATTATACACGATTAT-ACTCGCTCCAAGCAGTGGGAGGA-GA-ATTT-GGCCCAGCCA
GAGTGCATGTGCCCTTTCTCTCCAGACTTAAAGCAATAAAACAGACTTAGGTAAATTCTCAGATAA
GCGTGCATGTACCTTTTCTCTCAGATTTAAAGCAATTAAATAGACCTAGGTAAATTCTCAGATAA
CCCTGATGGCTATATTGATGTTTACAAGGGTTAGGACAATTCTTGATCTGACATGGAGAGATATAATG
CCCTGATGGCTATATTGATGTTTACAAGGGTTAGGACAATCCTTTGATCTGACATGGAGAGATATAATG
TCACTGCTAAATCAGACACTAACCCCAATGAGAGAAGTGCCACCATAACTGCAGCCTGAGAGTTTGGCG
TTACTGCTAAATCAGACACTAACCCCAATGAAAAAAGTGCTGCCATAACAGCAGCCTGAGAGTTTGGCG
ATCTCTGGTATCTCAGTCAGGTCAATGATAGGATGACAACAGAGGAAAGAGAATGATTCCCCACAGGCCA
AACTCTGGTATCTCAGTCAGGTCAATGATAGGATGACAACAGATGAAAGAGAATGATTCCCCACAGGCCA
GCAGGCAGTTCACAGTCTAGACCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGTCTCAGACAT
GCAGGCAGTTCACAGTCTAGACCCTCATTAGGACACAGAATCAGAACTTGGAGATTGGTGCCACAGACAT
TTGCTAACTTGTGTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGTCTATGAATTACTCAATGATGTCCA
TTGCTAACTTGGCTGCTAGAAGGACTAAGGAAAACTAGGAAGAAGCCCATGAATTATTCAATGATGTCCC
CCATAACACAGGGAAGGGAAGAAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAGGAAGCG
CTATAACACAGGGAAGGGAAGAAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGATTGAGGAAGCA
TGCTCTCTGTCACTGACTCTTCTGAAGGCCAATAATCTTAAAGCGTAAGTTTATCACTCAGTCAGCT
TACCTCCCTGTCACTGACTCTATTAAAGGCCAATAATCTTAAAGGATAAGTTTATCACTCAGTCAGCT
GCAGACATTAGAAAAAACTTCAAAAGTCTGCCGTAGGCCCGGAGCAAACTTAGAAACCCCTATTGAAC
GCAGAGATTAAGAAAAAACTTCAAAAGTATGCCTTAGGCCAGAGCAAACTTAGAAACCCCTACTGAAC
TGGCAACCTCGGTTTTTATAATAGAGATCAGGAGGAGCAGGCCGAACAGGACAAACGGGATTAAAAAA
TGGCAACCTCAGTTTTTATAATAGAGATCAGGAAGAGCAGG-GGAATGGGACAAATGGGATAAAAAAA
A-----GGCCACCGCTTTAGTCATGACCTCAGGCAAGTGGACTTTGGAGGCTCTGGAAAAGGGAAAA
AAAAAAAGGTGACTGCTTTAGTCGTGGCCCTCAGGCAAAATGGACTTTGGAGGCTCCAGAAAAGGGAAAA
GCTGGGCAAAATTGAATGCCTAATAGGCTTGCTTCCAGTGGGTCTACAAGGACACTTAAAAAAGATTG
GCTGAGCAAAATTGAATGCCTAACAGGGCTTGCTTCTAGTGTGGTCTACAAGGACACTTAAAAAAGATTG
TCCAAGTAGAAGTAAGCCGCCCTCGTCCATGCCCTTATTTCAAGGGAATCACTGGAAGGCCCACTGC
TCCAAGTAGAACAAGCTGCCCCCTTGCCATGCCCTTATGTCAAGGGAATCACTGGAAGGCCCACTGC
CCCAGGGGACAAAAGGTCTCTGAGTCAGAAGCCACTAACCAGATGATCCAGCAGCAGGACTGAGGGTGCC
CCCAGGAGATGAAGTCTCTGAGTCAGAAGCCACTAACCAGATAATCCAGCAGCAGGACTGAGGATGCC
TGGGCAAGCGCCATCCCATGCCATCACCTCACAGAGCCCTGGGTATGCTTGACCATGAGGGCCAGGA
CAGGCAAGCGCCAGCCCATGCCATCACCTCACAGAGCCCTGGGTATGCTTGACCATGAGGGCCAGGA
GGTT---GTCTCTGGACACTGGTGGCTTCTTAGTCTTACTCTTCTGTCCCGGACAACTGTCTCTC
GGTTCAGTGTCTCTGGACACTGGTATGCCCTTCTCAGTCTTACTCTCTGTCTGGACAACTGTCTCTC

FIGURE 7

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01/ TAAATCCCCATGGCCCTCCCTTATCATATTTTTCT
 02/ TAAATCCCC-TGGCCCTCCCTTATCATATTTTTCT
 03/ TAAATCCCCATGGCCCTCCCTTATCATATTTTTCT
 04/ TAGATCCTCATGGCCCTCC-TTGTATATTTTTTT

01/CTTTACTGTTCTTTTA-CCCTCTTTCACTCTCACTGCACCCCTCCATGCCGCTGTATGACC
 02/CTTTACTGTTCTCTTACCCCTTTCACTCTCACTGCACCCCTCCATGCCACTGCACCCCT
 03/CTTTACTGTTCTCTTA-CCCCCTTTCTCTCACTGCACCCCTCCATGCTGCTGTACAACC
 04/CTTTACTGTTCTCTTA-CCCCCTTTCACTCTCACTGAACCCCTCCATGCCACTGTACTACC

01/AGT-----AGCTCCCCTTACCAAGAGTTTCTATGGAGAATGCAGCGT
 02/GTCCATGCCCGTCTCATGCCAGTAGCTCCCCTTAGCAAGAGTTTCTATGGAGAATGCAGCGT
 03/AGC-----AGCTCCCCTTACCAAGAGTTTCTATGAAGAATGCGGCTT
 04/AGT-----AGCTCCCATTACCAAGAGCTTCTATGGACAATGCGGCTT

01/CCCGGAAATATTGATGCCCCATCGTATAGGAGTCTTTCTAAGGGAACCCACCTTCACTGC
 02/CCCGGAAATATTGATGCCCCATTGTATAGGAGTTTCTAAGGGAACCCACCTTCACTGC
 03/CCCGGAAATATTGATGCCCCATCAATAGGAGTTTCTAAGGGAACCCACCTTCACTGC
 04/CCTGGAAATATTGATGACCCATCGTATAGGAGTTTTCTAAGGGAACCCATTTTACCAC

01/CCACACCCATATGCCCCGCAACTGCTATCACTCTGCCACTCTTTGCATGCATGCAAATACTC
 02/CCACACCCATATGCCCCGCAACTGCTATCACTCTGCCACTCTTTGCATGCATGCAAATACTC
 03/CCACACCCATATGCCCCGCAACTGCTATCACTCTGCCACTCTTTGCATGCATGCAAATACTC
 04/CCACACCTATATGACCC-----

01/ATTATTGGACAGGAAAAATGATTAATCCTAGTTGTCCTGGAGGACTTGGAGTCACTGTCTGT
 02/ATTATTGGACAGGAAAAACGATTAATCCCAGTTGTCCTGGAGGACTTGGAG-----
 03/ATTATTGGACAGGAAAAATGATTAATCCTAGTTGTCCTGGAGGACTTGGAGCCACTGTCTGT
 04/-----

01/TGGACTTACTTCACCCAACTGGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAAGAGA
 02/--GACTCACTTCACTCATACAGTATGTCTGATGGGGGTGGAGTTCAAGATCAGGCAACAGA
 03/CGGACTTACTTCACCCATACTGGTATGTCTGAGGGGGTGGAGTTCAAGATCAGGCAAGAGA
 04/-----

01/AAAACATGTAAAGAAGTAATCTCCCAACTCACCCGGGTACATGGCACCTCTAGCCCCCTACA
 02/AAAACACATAAAGGAAGTAATCTCCCAACTGACCTGGGTACATAGCACCCCTGGCCCCCTACA
 03/AAAACATGTAAAGGAAGTAACCTCCCAACTGACCCGGGTACATAGCACCCCTAGCCCCCTACA
 04/-----

01/AAGGACTAGATCTCTCAAACTACATGAAACCCTCCGTACCCATACTCGCCTGGTAAGCCTA
 02/AAGGACTAGATCTCTCAAACTACATGAAACCCTCCATACCCATACTGGCCTGGTAAGCCTA
 03/AAGGACTAGATCTCTTAAACTACATGAAACCCTCCATACCCATACTGCCTGGTAAGCCTA
 04/-----

01/TTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGCCCAAACCCCTACTAACTGTTGGAT
 02/TTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGCCCAAACCCCTACTAACTGTTGGAT
 03/TTTAATACCACCCTCACTGGGCTCCATGAGGTCTCGGTCCAAACCCCTACTAACTGTTGGTT
 04/-----

01/ATGCCTCCCCCTGAACTTCAAGCCATATGTTTCAATCCCTGTACCTGAACAATGGAACAAC
 02/GTGCCTCCCCCTGCACTTTAGGCCATACATTTCAATCCCTATACCTGAACAATGGAACAAC
 03/GTGCCTCCCCCTGTATTTCAAGCCATGCATTTCAATCCCTGTACCTGAACAATGGAACAAC
 04/-----TGCACTTCAAGCCATACATTTCAATCCCTGTA-----

FIGURE 8.1

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01/TCAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCTCTTGTTTCCAATCTGGAAATA
 02/TCAGCACAGAAATAAACACCACTTCTGTTTTAGTAGGTCCTC---TTTCCAATCTGGAAATA
 03/ACAGCACAGAAATAAACACCACTTCCGTTTTAGTAGGACCTCTTGTTTCCAATCTGGAAATA

01/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTACATACACAACCAACTCCCA
 02/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTATAGACACAGCCAACTCCCA
 03/ACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTGTAGACACAACCAACTCCCA
 04/-----

01/ATGCATCAGGTGGGTAACCTCCTCCACACAAATAGTCTGCCTACCCTCAGGAATATTTTTTG
 02/ATGCATCAGGTGGGTAACCTCCTCCACACGAATAGTCTGCCTACCCTCAGGAATATTTTTTG
 03/ATGCATCAGGTGGGTAACCTCCTCCACACGAATAGTCTGCCTACCCTCAGGAATATTTTTTG
 04/-----

01/TCTGTGGTACCTCAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCA
 02/TCTGTGGTACCTCAGCCTATCATTGTTTGAATGGCTCTTCAGAATCTGTGTGCTTCCTCTCA
 03/TCTGTGGTACCTTAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCA
 04/-----

01/TTCTTAGTGCCCCCTATGACCATCTACACTGAACAAGATTTATACAGTTATGTCATATCTAA
 02/TTCTTAGTGCCCCCTATGCCCCATCTACACTGAACAAGATTTATACAATCATGTCATACCTAA
 03/TTCTTAGTGCCCCCTATGACCATTTACACTGAACAAGATTTATACAATTATGTTGTACCTAA
 04/-----

01/GCCCCGCAACAAAAGAGTACCCATTCTTCCTTTTGTATAGGAGCAGGAGTGCTAGGTGCAC
 02/GCCCCGCAACAAAAGAGTACCCATTCTTCCTTTTGTATTGGAGCAGGAGTGCTAGGCGGAG
 03/GCCCCACAACAAAAGAGTACTCATTCTTCCTTTTGTATCGGAGCAGGAGTGCTAGGTGGAC
 04/-----

01/TAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAACTATCTCAAGAA
 02/TAGGTACTGGCATTGGCGGTATCACAACCTCTACTCAGTTCTACTACAACTGTCTCAAGAA
 03/TAGGTTCTGGCATTGGCGGTACCACAACCTCTACTCAGTTCTACTACAACTATCTCAAGAA
 04/-----

01/CTAAATGGGGACATGGAACGGGTGCGCGACTCCCTGGTCACCTTGCAAGATCAACTTAACTC
 02/CTTAAAGGTGACATGGAATGGGTGCGTGATACCCTGGTCACCTTGCAAGATCAACTTAACTC
 03/CTCAATGGTGACATGGAATGGGTGCGCGACTCCCTGGTCACCTTGCAAGATCAACTTAACTT
 04/-----

01/CCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGG
 02/CCTAGCAGCAGTAGTCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCGGAAAGCGGGG
 03/CCTAGCATCAGTAGTCCTTCAAAATTGAAGAGCTTTAGACTTGCTAACCTCTGAAAGAGGGG
 04/-----

01/GAACCTGTTTATTTTTAGGGGAAGAATGCTGTTATTATGTT-----
 02/GAACCTTTTTATTTTTAGAGGAAAAATGCTGTTGTTATGTT-----
 03/GAAGCTGTTTATTTTTAGGGGAAGAATGTTGTTATTATGTTATTTAGCGGAAGAATGTTGT
 04/-----

01/-----AATCAATCCGGAATCGTCACTGAGAAAGTTAAAGAAATTCGAGATCGAATACA
 02/-----AATCAATCCGGAATCATCACCGAGAAAGTTAAAGAAATTCAGGTCGAATATA
 03/TATTATGTTAATCAATCCTGAATTGTACAGAGAAAGTTGAAGAAATTCGAGATTGAATACA
 04/-----

01/ACGTAGAGCAGAGGAGCTTCGAAA-CACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
 02/ACGTAGAGCAAAGGAGCTGCAAA-CACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
 03/ACGTAGAACAGAGGAGCTTCAAAAACACCAGACCCTGGGGCCTCCTCAGCCAATGGATGCCCT
 04/-----

FIGURE 8.2

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01/ GGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTCTTTGGACCCCTGTA
02/ GGATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGTTACTCCTCTTTGGACCCCTGTA
03/ GGATTCTCCCCTTCTTAGGATCTCTAGCAGCTCTAATATTGATACTCCTCTTTGGACCCCTGTA
04/ -----

01/ TCTTTAACCTCCTTGTTAACTTTGTCTCTTCCAGAATCGAAGCTGTAAACTA-----
02/ TCTTTAACCTCCTTGTTAAGTTTGTCTTTTCCAGAATCGAAGCAGTAAACTACAAATCGTTT
03/ TCTTTAACCTCCTTGTTAAGTTTGTCTCTTCCAGAATCAAAGTTGTAAAGCTACAAATCGTTT
04/ TCTTTAACCTCCTTGTTAAGCTTGTCTCTTGCAGAATCGAAGCTGTAAACTACAAATGCTTG

01/ --CAAATGGAGCCCAAGATGCAGTCCAAGACTAAGATCTACCGCAGACCCCTGGACCGGCCTG
02/ TTCAAATGGAGCCCCAGATGCAGTCCATGAGTAAATCTACACGGACCCCTGGACCGGCCTG
03/ TTCAAATGGAACCCAGATGAAGTCCATGACTAAGATCTACCGTGGACCCCTGGACCGGCCTA
04/ TTAATAAGAGCCCCAGATGCAGTCCATGGCTAAGATCTACACGGACCCCTGGACCGGCCTG

01/ CTAGCCCACGATCTGATGTTAATGACATCAAAGGCACCCCTCCTGAGGAAATCTCAGCTGCAC
02/ CTAGCCCATGCTCTGATGTTAATGACATCAAAGGCACCCCTCCCGAGGAAATCTCAACTGCAC
03/ CTAGCCCATGCTCCAATTGTAATGATATCGAACGCACCCCTCCCGAGGAAATCTCAACTGCAC
04/ CTAGCCCATGCTCTGATGTTGATGACATTGAAGGCACGGCTTCCGAGGAAATCTCAACTGCAC

01/ AACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCCCC
02/ AACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGTGGTTGTTGGCCAACCTCCCC
03/ AACCCTACTATGCCCCAATTCGCGCAGGAAGCAGTTAGACTGGTCGTCAGCCAACCTCCCC

04/ GACCCCTACTACACCCCAATTTAGCGGGAAGCAATTAGAGCAGCCTATGGCCACCTCCCC

FIGURE 8.3

09/719554-01301

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CTTCCCCAACTAATAAGGACCCCCCTTCAACCCAAACAGTCCAAAAGGACATAGACAAAGGA 3
 CTTCCCCAACTAATAAGGACCCCCCTTCAACCCAAACAGTCCAAAAGGACATAGACAAAGGA 4
 CTTCCCCAACTAATAAGGACCCCCCTTCAACCCAAATGGTCCAAAAGGAGATAGACAAAGG 5
 CTTCTCCAATAATAAGGACCCCCCTTCAACCCAAATGGTCCAAAAGGAGATAGACAAAGG 6
 CTTCCCCAAATAATAAGAACCCCCCTTCAACCCAAACGGTCCAAAAGGAGATAGACAAAGG 7

GTAACAATGAACCAAAGAGTGCCAATATTCCCTGGTTATGCACCCTCCAAGCGGTGGGAG-- 3
 GTAACAATGAACCAAAGAGTGCCAATATTCCCTGGTTATGCACCCTCCAAGCGGTGGGAG-- 4
 GTAACAGTGAACCAAAGAGTGCCAATATTCCCAATTATGACCCTCCAAGCAGTGGGAGGA 5
 GTAACAATGAACCAAAGAGTGCCAATATTACAGATTATACTCGCTCCAAGCAGTGGGAG-- 6
 GTAACAATAACCAAAGAATGCCAATATTCCCGATTATGCCCCCTCCAAGCGGTGGGAG-- 7

A-AGAATTCGGCCCAGCCAGAGTGTCATGTACCTTTTTCTCTCTCAC-ACCTGAAGCAAATTAAA 3
 A-AGAATTCGGCCCAGCCAGAGTGTCATGTACCTTTTTCTCTCTCAC-ACCTGAAGCAAATTAAA 4
 AGAGAATTCGGCCCAGCCAGAGTGTCATGTGCCTTTTTCTCTCCAG-ACCTAAAGCAAATAAAA 5
 -GAGAATTTGGCCCAGCCAGCGTGCATGTACCTTTTTCTCTCTCAG-ATTTAAAGCAAATTAAA 6
 -GAGAATTCGGCCCAGCCAGAGTGTCACGTACCTTTTTCTCTCTCTAGACTTTAAA----TTAAA 7

ATAGACNTAGGTNAATTNTCAGATAGCCCTGATGGYTATATTGATGTTTTACAAGGATTAGGA 3
 ATAGACXTAGGTXAATTXTCAGATAGCCCTGATGGXTATATTGATGTTTTACAAGGATTAGGA 4
 ACAGACTTAGGTAAATTCTCAGATAACCTGATGGCTATATTGATGTTTTACAAGGGTTAGGA 5
 ATAGACCTAGGTAAATTCTCAGATAACCTGATGGCTATATTGATGTTTTACAAGGGTTAGGA 6
 ATAGACCTAGGTAAATTCTCAGATAACCTAATGGCTATATTGATGTTTTACAAGGGTTAGGA 7

TTCTGAGTTCCTGCACTAACCTCAAAT 1
 CAATCCTTTGATCTGACATGGAGAGATATAATATTACTGCTAAATCAGACGCTAACCTCAAAT 3
 CAATCCTTTGATCTGACATGGAGAGATATAATATTACTGCTAAATCAGACGCTAACCTCAAAT 4
 CAATCTTTGATCTGACATGGAGAGATATAATGTCACTGCTAAATCAGACACTAACCCCAAAT 5
 CAATCCTTTGATCTGACATGGAGAGATATAATGTTACTGCTAAATCAGACACTAACCCCAAAT 6
 CAATCCTTTGATCTGATATGGAGAGATATAATGTTACTGCTAAATCAGACACTAACCCCAAAT 7

GAGAGAAGTGCCGCATAACTGCAACCCAAAGAGTTTGGCGATCCCTGGTATCTCAGTCAGGTC 1
 GAGAGAAGTGCTGCCATAACTGGAGCCCAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC 3
 GAGAGAAGTGCTGCCATAACTGGAGCCCAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC 4
 GAGAGAAGTGCCACCATAACTGCAGCCTGAGAGTTTGGCGATCTCTGGTATCTCAGTCAGGTC 5
 GAAAAAAGTGCTGCCATAACAGCAGCCTGAGAGTTTGGCGAACTCTGGTATCTCAGTCAGGTC 6
 GACAGAAGTGTCGCCGTAACCTGGAGCCCAGAGTTTGGCAATCTCTGGTATCTCAGTCAGGTC 7

AATGACAGGATGACAACAGAGGAAAGATAATGATTCCCCACAGGCCAGCAGGCAGTTCACAGT 1
 AATGATAGGATGACAACGGAGGAAAGAGAACGATTCCCCACAGGGCAGCAGGCAGTTCACAGT 3
 AATGATAGGATGACAACGGAGGAAAGAGAACGATTCCCCACAGGGCAGCAGGCAGTTCACAGT 4
 AATGATAGGATGACAACAGAGGAAAGAGAATGATTCCCCACAGGCCAGCAGGCAGTTCACAGT 5
 AATGATAGGATGACAACAGATGAAAGAGAATGATTCCCCACAGGCCAGCAGGCAGTTCACAGT 6
 AATGATAGGATGACAACAGAGGAAAGAGAACGATTCCCCACAGGCCAGCAGGCAGTTCACAGT 7

GTAGACCCTCATTAGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTGCTAACT 1
 AACT 2
 GTAGCTCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTACTAACT 3
 GTAGCTCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTT 4
 CTAGACCCTCATTGGGACACAGAATCAGAACATGGAGATTGGTGCTGCAGACATTTGCTAACT 5
 GTAGACCCTCATTAGGACACAGAATCAGAACATGGAGATTGGTGCCACAGACATTTGCTAACT 6
 GTAGACCCTCACTGGGACACAGAATCAGAACATGGAGATTGGTGCCGCAGACATTTGCTAACT 7

FIGURE 9.1

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TGCGTGCTAGAAGGACTAAGGAAAACCTAGGAAGA----TATGAATTATTCAATGATGTCCACT 1
TGCGTGCTAGAAGGACTAAGGAAAACCTAGGAAGA---CTATGAATTATTCAATGATGTCCACT 2
TGCGTGCTAGAAGGACTAAGGAAAACCTAGGAAGA---CTATGAATTATTCAATGATGTCCACT 3
TGTGTGCTAGAAGGACTAAGGAAAACCTAGGAAGAAGTCTATGAATTACTCAATGATGTCCACA 5
TGCGTGCTAGAAGGACTAAGGAAAACCTAGGAAGAAGCCCATGAATTATTCAATGATGTCCCT 6
TGCGTGCTAGAAGGACTAAGGAAAACCTAGAAAAGAAGCCTGTGAGTTATTCAATGATGTCCACT 7

ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG 1
ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG 2
ATAACACAGGGGAAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG 3
ATAACACAGGG-AAGGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAGGCATTGAG 5
ATAACACAGGG-AAAGGAAGAAAATCCTACTGCCTTTCTGGAGAGACTAAGGGAAGGATTGAG 6
ATAACACAGGG-AAAGGAAGAAAATCCTACCGCCTTTCTGGAGTGAATAACGGAGGCATTGAG 7

GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGAAAAGGGAAAAGTTGGGAAAAGTA 1
GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGAAAAGGGAAAAGTTGGGCAAATTG 2
GAAGCATACC---AGGCAAGTGGACATTGGAGGCTCTGAAAAGGGAAAAGTTGGGCAAATTG 3
GAAGCGTGCC232AGGCAAGTGGACTTTGGAGGCTCTGAAAAGGGAAAAGCTGGGCAAATTG 5
GAAGCATACC238AGGCAAGTGGACTTTGGAGGCTCCAGAAAAGGGAAAAGCTGAGCAAATTG 6
GAAGCATACC233AGGCAAGCGGACTTTGGAGGCTCTGAAAAGGGAAAAGCTAGGCAAATCA 7

TATGTCTAATAGGGCTTGCTTCCAGTGTGGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA 1
AATGCCTAATAGGGCTTGCTTCCAGTGCAGTCTACAAGGACGCTTTAGAAAAGATTGTCC-AA 2
AATGCCTAA 3
AATGCCTAATAGGGCTTGCTTCCAGTGCAGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA 5
AATGCCTAACAGGGCTTGCTTCTAGTGTGGTCTACAAGGACACTTTAAAAAAGATTGTCC-AA 6
AATGCCTAATAGGGTTTGCTTCCAGTGCAGTCTACAAGGACACTTTAAAAAAGATTGTCCAAA 7

-TAGAAATAAGCCACCACCTCGTCCATGCCCCCTTATGTCAAGGGAATCACTGGAAGGCCCACT 1
GTAGAAATAAGCCGCCCC-TCGTCCATGCCCCCTTATGTCAAGGGAATCACTGGAAGGCCACT 2
GTAGAAGTAAGCCGCCCCCTCGTCCATGCCCCCTTATTTCAAGGGAATCACTGGAAGGCCCACT 5
GTAGAAACAAGCTGCCCCCTTGCTCCATGCCCCCTTATGTCAAGGGAATCACTGGAAGGCCCACT 6
-TAGAAATAAGCCGCCCCCTCGTCCATGCACCTCGTGTCAAGGGAATCACTGTAAGGCCCACT 7

GCCCCAGGGGATGAAGGTCTCTGAGTCAGAAGCCACTAACCAGATGA 1
GCCCCAGGGGACGAAGGTCTCTGAGTCAGAAGCCACTAACCCTGATGA 2
GCCCCAGGGGACAAAGGTCTCTGAGTCAGAAGCCACTAACCAGATGA 5
GCCCCAGGAGATGAAGGTCTCTGAGTCAGAAGCCACTAACCAGATAA 6
GCCCCAGGGGACGTAGGTCTCTGAGTCAGAAGCCACTAACCAGATGA 7

FIGURE 9.2

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RTPLSTQTVQKDIDKGVNNEPKSANIPWLCTLQAVGEEFGPARVHVPFSLSHLKQIKIDG SDSPDG
- = == ===== = ===== = ===== = ===== = == ==
KDPSTQMVMQKEIDKRVNSEPKSANIPQLPLQAVGGREFGPARVHVPFSLPDLKQIKTDLGKFSDNPDG

YIDVLQGLGQSFDLTWRDIILLNQTILTSNERSAAITGAREFGNLWYLSQVNDRMTEERERFPTGQQ
===== ----- ===== ----- ===== ----- =====
YIDVLQGLGQFFDLTWRDIMSLNQTILTPNERSATITAA~~X~~FGDLWYLSQVNDRMTEEREX~~F~~PTGQQ

AVPSVAPHWDTESEHGDWCRRHLLTCVLEGLRKTRK TMNYSMMSTITQ GK
===== -----
AVPSLDPHWDTESEHGDWCRRHLLTCVLEGLRKTRKKSMMNYSMMSTITQGR

FIGURE 1009719554-01501
FIGURE 10

FIGURE 11

[illegible]

Figure 1 displays 12 Western blot panels showing protein levels in H1299 cells. The proteins analyzed are p53, p21, p16, p14, p15, p18, p19, p20, p22, p24, p27, and p28. Each panel includes a 'Control' lane and a 'Treated' lane. Molecular weight markers are indicated on the right of each panel. The blots show varying levels of protein expression, with some proteins showing significant changes upon treatment.

FIGURE 12

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agttgcaattccttgccctcaactctgagagaaaccccagccacatctccagcaaaacaaga
|||||
agttgcaattccttgccctccactgtgagacaaaccccagacacatctccagcacacaaga 2299

acttcaaaacacctgaactgcagcagccaggcggttctccaggaccacctccccaggat
|||||
acttcgaaatgcctcaacctcaggtgccagggggttctccagaaccttctccccaggag 2359

cttgcttcaagtgccggaaatctgaccattggggccaaggaatgcctgcagcccaggattc
|||||
cttgctacaagtgccagaaatctggccactggggccaaggaatgccacagaccaggattc 2419

ctcctaagccacgtcccatcttgctgaggacccccactggaaatcggaactgtccaactcacc
|||||
ctcctaagctgtatcccatctctgtgggacccccactaaaaatcagactgttcaactcacc 2479

cggcagccaatcccagagcccctggaaactctggccaaggctctctgactgactccttcc
|||||
tggcagccacttccagagcccctggaaactctagcccaaggctctctgactgaccttct 2539

cagatcttctcggttagcagctgaagactgacactgcccgatcacttcagaagtccct
|||||
gagatcttcttggttagcagctgaagactgacactgccagatcgctcggaagcctaca 2599

ggaccatcacggatactgagcttcaggtaactctcacagtggaggctaagtccatccct
|||||
ggaccatcacagat-----gctccaggtaactctcacagtagagggttaagtctgtccct 2654

gtttaatcgatacaggggctaccactccacatcaacttcttttcaagggcctgtttccc
|||||
tcttaatcaatatggaggctaccactgcacattaccttcttttcaagggcctgtttcct 2714

tttccccataactgttggtggtattgacggccaagcttcaaaaccccttaaaactcccc
|||||
ttgcctccataactgttggtggtattgacggccaggcttctaaacctcttaaaactcccc 2774

cactctggtgccaaacttggaacaacttcttttatgcaactctttttcagttatcctcacct
|||||
aactctagtagcaacttagacaataactcttttaagcactcttttttagttatccccactt 2834

gcccagttcccttattaggccgagacattttaaccaaattatctgcttccccgactattc
|||||
gcccagttcccttatgaggccgagacacttcaactaaattatctgcttccctgactattc 2894

ctgggctacagccacatctccttgccgccttcttcccaacccaaagcctccttcatatc
|||||
ctggactacagctacatctcattgctgccttcttcccaatccaaagcctccttgcac 2954

ttcctctcatatccccccaccttaaccacaaagtatgggacacctctactccctccctgg
|||||
ttcttgc---atcccccaaccttaaccacaaagtataagatacctctattccctccttgg 3011

FIGURE 13.1

FIGURE 13.2

1997-1998		1998-1999		1999-2000		2000-2001		2001-2002		2002-2003		2003-2004		2004-2005		2005-2006		2006-2007		2007-2008		2008-2009		2009-2010		2010-2011		2011-2012		2012-2013		2013-2014		2014-2015		2015-2016		2016-2017		2017-2018		2018-2019		2019-2020		2020-2021		2021-2022		2022-2023		2023-2024		2024-2025		2025-2026		2026-2027		2027-2028		2028-2029		2029-2030		2030-2031		2031-2032		2032-2033		2033-2034		2034-2035		2035-2036		2036-2037		2037-2038		2038-2039		2039-2040		2040-2041		2041-2042		2042-2043		2043-2044		2044-2045		2045-2046		2046-2047		2047-2048		2048-2049		2049-2050		2050-2051		2051-2052		2052-2053		2053-2054		2054-2055		2055-2056		2056-2057		2057-2058		2058-2059		2059-2060		2060-2061		2061-2062		2062-2063		2063-2064		2064-2065		2065-2066		2066-2067		2067-2068		2068-2069		2069-2070		2070-2071		2071-2072		2072-2073		2073-2074		2074-2075		2075-2076		2076-2077		2077-2078		2078-2079		2079-2080		2080-2081		2081-2082		2082-2083		2083-2084		2084-2085		2085-2086		2086-2087		2087-2088		2088-2089		2089-2090		2090-2091		2091-2092		2092-2093		2093-2094		2094-2095		2095-2096		2096-2097		2097-2098		2098-2099		2099-2100		2100-2101		2101-2102		2102-2103		2103-2104		2104-2105		2105-2106		2106-2107		2107-2108		2108-2109		2109-2110		2110-2111		2111-2112		2112-2113		2113-2114		2114-2115		2115-2116		2116-2117		2117-2118		2118-2119		2119-2120		2120-2121		2121-2122		2122-2123		2123-2124		2124-2125		2125-2126		2126-2127		2127-2128		2128-2129		2129-2130		2130-2131		2131-2132		2132-2133		2133-2134		2134-2135		2135-2136		2136-2137		2137-2138		2138-2139		2139-2140		2140-2141		2141-2142		2142-2143		2143-2144		2144-2145		2145-2146		2146-2147		2147-2148		2148-2149		2149-2150		2150-2151		2151-2152		2152-2153		2153-2154		2154-2155		2155-2156		2156-2157		2157-2158		2158-2159		2159-2160		2160-2161		2161-2162		2162-2163		2163-2164		2164-2165		2165-2166		2166-2167		2167-2168		2168-2169		2169-2170		2170-2171		2171-2172		2172-2173		2173-2174		2174-2175		2175-2176		2176-2177		2177-2178		2178-2179		2179-2180		2180-2181		2181-2182		2182-2183		2183-2184		2184-2185		2185-2186		2186-2187		2187-2188		2188-2189		2189-2190		2190-2191		2191-2192		2192-2193		2193-2194		2194-2195		2195-2196		2196-2197		2197-2198		2198-2199		2199-2200		2200-2201		2201-2202		2202-2203		2203-2204		2204-2205		2205-2206		2206-2207		2207-2208		2208-2209		2209-2210		2210-2211		2211-2212		2212-2213		2213-2214		2214-2215		2215-2216		2216-2217		2217-2218		2218-2219		2219-2220		2220-2221		2221-2222		2222-2223		2223-2224	
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atataaaactcacaaaaggaaacctagctgaccccatagattctaaatcctttcccccactc
 |||||
 atataaaactcacaaaaggaaacctagttgaccccatagatcctaaatcgtttcccccactc 3898

ctctttccattccttgaagacagcttttagagactgctccacactagctctccctgtctc
 |||||
 ctctttccattccttgaagacagcttttagagactgtctccactctagctctccctgactc 3958

atcccaacccttttcattacacacagccgaagtgcagggctgtgcagtcggaattcttac
 |||||
 atcccaacacttttcattacacacagctgaagtgcagggctgtgcagtcagaattcttac 4018

acaaggaccgggacccatgcctgtagccttttgtccaaacaacttgaccttactgtttt
 |||||
 acaaggaccgggatcgcatcctgtagccttttgtccaaacaacttgaccttactgtttt 4078

aggctcgccatcatgtctccatgcggtagcttccgctgcctaataacttttagaggccct
 |||||
 aggctggccatcatgtctccatgcagcgtctgctgccaccctaataacttttagaggccct 4138

caaaatcacaaactatgtctcaactcactctctacagctctcacaacttccaaaatctatt
 |||||
 caaaatcacaaactatgtctcaactcattctctacagctctcacaatttccaaaatctatt 4198

ttctttctcacacctgacgcataatactttctgtccccgggtccttcagctgtattcact
 |||||
 ttcttctctcacacctgacacataatactttctgtccccgggtccttcagatataactcact 4258

ctttgttgagtctcccacaattaccattcttctctggccagacttcaatctggcctcca
 |
 c--catttattctcccacaattaccattattctctggcctggacttcaatccggcctcca 4316

cattattctggataccacacctgaccctgatgattgtatgtctctgatctacctgacatt
 |||||
 cattattctggataccatacctgaccctcatgactgcatctctctgatccacctgacgtt 4376

caccacatttccccatatttcttctttctgttctctcatgttgatcacatttggtttac
 |||||
 caccacatttccccacatttcttctgtccctgtttctcaccctgatcacacttggtttat 4436

tgacggcagttccaccaggcctgatcgccactcaccagcaaaggcaggctatgctat
 |||||
 tgatggcagttccaccaggcctaatacgccactcaccagcaaaggcaggatagctat 4493

gaactgattgccttaactcgggccttcaactcttgcaaagggactacacgtcaatatattat
 |||||
 gaactagttgccttaattcaagccctcactcttgcaaaaggactacgtgtcaatatctat 4553

actgactctaaatatgccttccatatcttgcaccaccatgctgttatatgggctgaaaga
 |||||
 actgattctaaatatgcctttcatattctgcaccaccatgcggtcatatgggctgaaaga 4613

ggtttctcactacgcaagggtcctccatcattaatgcctctttaataaaaaactcttctc
 |||||
 ggtttctcactacacaagtgtcctccatcattaatgcctctttaagaaaa-ctctgctc 4672

FIGURE 13.3

09719554-011801

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aaggctgctttacttccaaaggaagctggagtcacacactgcaagggccaccaaaggcg
|||||
aaggctgctttacttccaaaggaagctggggtcattcactgcaaggggcatcaaaagact 4732

tcagatcccattactctaggaatgcttatgctgataaggtagctaaagaagcacctagc
|||||
tcagatcccattgctctaggcaatgcttatgctgataaggtggctagacaagcagctagc 4792

gttccaaacttctgtccctcatggccagtttttctccttcccatcagtcattcccacctac
|||||
tctccaaacttttgtccctcatggccagtttttctccttcacatccgtcactcccacctac 4852

tccccattgaaacttccgcctatcaatctcttctcacacaaggcaaatggttcttagac
|||
tccacagctgaaacttccacctatcaagctcttcccccgcaaggtaaatggttcttagac 4912

caaggaaaatatctccttccagcctcacaggccattctattctgtcatcatttcataac
|||||
caaggaaaatatctccttccagcctcacaggccattctattctgtcgtcatttcataac 4972

ctcttccatgtaggttacaagccactagtcacactcttagaacctctcatttcctt-cca
||
cttttccatgtaggttacaagccactagcctgtctcttaggacctctcatttcctttcca 5032

tcgtggaaacatatcctcaaggaaatcacttctcagtggttccatctgctattctactacc
||
tcagtgaaatctatcctcaaggagatcacttctcagtggttccatctgctattctgctacc 5092

cctcagggattgttcaggcccccctcccctccctacacatcaagctcggggatttgccct
|||||
cctcagggattgttcaggccctcctccccttccctacacataaagctcggggatttgccct 5152

gcccaggactggcaaatgactttactcacatgcccagtcaggaaactaaaaacctc
|||||
gcccaggactggcaaatgactttactcacatgcccgggtcagaaaactaaaaatatctc 5212

ttggtctgggtagacactgtcactggatgggtagaggcctttcccacagggtctgagaag
||
ttagtctgggtagacactttcactgggtgggtagaggcctttcccatagagtctgagaag 5272

gccactgcagtcatttcttcccttctgtcagacataattccttgggttgcccttcccacc
|||||
gccaccgcggtcatttcttcccttctgtcagacataattccttgggttgcccttcccttc 5332

tctatacagtccaataacggagcagcctttattagtcaaatcacctgagcagtttttcag
|||||
tctatacagtctgataacggaccagcctttactagttaaatcacccaagcagtttttcag 5392

gctcttggtattcagtggaaccttcgtacccttactgtcctcaatcttcaggaaaggta
|||||
gctcttggtattcagtggaaccttcataatcccttaacatcctcaatcttcaggaaaggta 5452

gaatggactaatggtcttttaaaaacacacccaccaaactcagcctccaacttaaaaag
||
aaaccgactaatggtcttttaaaagacacacctcaccaagctcagcctccaacttaaaaag 5512

FIGURE 13.4

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TGCCTTTATTTCCGTAGGCTGGTTCATATGGCGCTAGCACTCACATAAAGCTACCGAGGAG
 AGCGAATGAAACCAAAATCACTTTACCTTCACAGCACGAGGCCGTGCTCCCTCTCGATAT
 TTGGCCCCGTGTGTGCGCATACCGCCCTCTGGACGTGGTGATCAAATAAACTCCCTAGCTCC
 CCGCCGCTCGACGCCATCTTGCCTACTTTGATCCTCGCAGGGAGGACAACATCCGCCCTA
 CTGAGCTCCCTTTTATCCAATAAGAGAGCGGGATGAGTTAAGGAGTGCCAGGATTGGCTG
 GAGAATCGACAGCGTCCGCCATCGTTTCTGCGTGCGAAGATTGATGAACGAGGTGCCG
 CCCCCGAGCGGCTCGGCCGAGAGGCGCGGTGGTGACAGAAGCTTTCTGTCCCACCCAC
 TACAGGCTTACGGCAGGATGCGCAGCGGGGAGAGGGGGCGGGGCCGAGGGGGCGGGGCC
 GATCGATCTCCTCCGGCTCCGACGTCTCCTCGGCTGCGGGTCCCGGGTCCCTTTGCGGCGC
TAGGTTGGGCGAACCAGAGCGACGCTCCGGGACGATGTGGGGCAGCGATCGCCTGGCGG
GTGCTGGGGGAGGCGGGGCGGCAGTGACTGTGGCCTTCACCAACGCTCGCGACTGCTTCC
TCCACCTGCCGCGCGTCTCGTGGCCCGAGCTGCATCTGCTGCAGGTAACCTGCCGGCCCC
 GAGCCACCTGATCTTCAGCCTGGGGTCCGACGAGGCCGAAGCCTCTCAGGGACGCGGCGG
 GACACCGGCTGCCACCCGGGCGCCGCGAAGCGCGCAGAGATCAGGGTCCCTCGACGGCA
 GGGCCCTTCTGGGTAGTCTCTGGATCCCACAAGTCCAGTGCAGCCCTGGGCTCGTCTTAT
 CCCAGGTCTTTTCACTTGGTGAAACTGAACCTAGAAACGTCCTAATATTCTACCACTGTT
 TTTATAAATATTCTTATTCAGGCTGGAAAAGCTCCTGAGAAGTGTTTGTGTTTTATTA
 TTTTAAAAGTGTTTTCTTGCCAGCCATTTCCAGTTAACCTGCGCTGCTGCCGTCCGGG
 CCGCGAGAGCGGGACGCGAGAGTTGTTGGCGGAGCCCTGTGCGTTCCCGGGGACTAAGCA
 CCGCGTCCCATGAGCGGAAAGGTTAATACAATGATGGTTCTGCCCTGCGTCTGCTGACGC
 GGAACACAGCTGTAGTGTGTTAGGAACACATAACGTAGTTAAGATCACTTGAAGCTCTGC
 GATCAGTCGCCCCCTCTGGACGTTGTGGTTAGGATGTTTCACAGTTCTAACCAGTGGTGA
 GATACAGCGTCCATATTTTCATAATTAATAAATAGAGGCACATGGTCTCACGAGTTTGAGT
 GTACTTATGGGGGCAAAAGGACGGCGTATTTGAAATCCTCATAAATCCTGGATGCATGGT
 ACCCACCAGTGGGCTAATCTATGCAATGAATAGAGTTTGCAATAATTTCAAGCATCCCTTC
 TTTCCACTTGAGTTACTTCCCCATACCTAGGGGAAGATATTTTGGTCCACTGAAAACAT
 GAGTTCAGCAGAATCCTCCTATCATCGTCTGTTATTATTTTTTACCACTAAGTAGACAATC
 TTTTGGTTTTTGTATGGGCTTTATGGCTAGAGACAAATCAGTCACTGTACCAAGTTCAG
 GTAGAAGTTGGTTCACTGCTCTGTGAGCTTCGATGGGATTTTTCAACATGTTTTTCAATC
 TGCACCTAATAGTAGGAATGCTTTCTTACAGTAACCTCTAATTTGATCCTAAGATGTAGTT
 GTTACCTTACATTCACTCACTGTTTAAAGAATTTAGTGGTCTTGATCTTTGTTTTAAATTT
 GAGCCTTCGGGAAGTACTTTATAAGAATTAATTCATGCATATCTTTTTGAAATGTAAATGT
 CTTTAGCCCTGGAACAAATGCTGTTTCTGTTTCCAGCCATATTAGCAGAATAGGTCAACT
 TTACTTTCTAATTATCAATGTAATAAGTTTATTACTTTATAGATTCCATAAATCTATACA
 TTTATTCTCGATGAATTATATAAATTTATAGAATTTATGTTTTATAGAAAATTTGGAAA
 GCATGGAAAATTTATTAACAAGAAAATAAGTTACCCATAATCCAGAACTTAGAGGTGACT
 AATGTTGACAGTTTGGATCAAATCTTCCAGTTTTGTTTCTAATCTTTATTTTAACATAA
 ATGAGGTCTGTATACACACGTACAGTTTTGTGTCTGCTGGTGTTTTTATTTAATGTTATTA
 TGAGTGTTTTATTTTGTAAAGGTCATCATTTTAAAGTTGTTAATTAGTATTCTAGCACA
 AATTTGCCATAATTTATTTAATGTTTACTATGATTGACCATTTAGATTGTACTTAATTT
 TTAGGCATTAGAAGTGATAAACTATATTTTAAATCAGACGTTGAAAATAACACATCTTTGT
 TTAGAAAACATCATTTTATTTCTGGTTGTCTAGGATAGATTCCCAGAATCTTGGGTTAG
 AGGCCATAGATAATTATGAAAGCAGAAAGATTCAAGTTGGGAGTTAATACTTGAATTA
 CTTTATTTGGGGTGAAGCATTGAGTGCATAATACAGATCATGCAGTAATGGGAAGAAGG
 TTGGAACAATGGTTTTCTGGCCTATGTCAGACTTACCTTGAAGCTTTTAAGAATACAGAT
 GTTCTGATCAACCCCTCAGACCTATTAAATCAGACCTAAATCTTAGGGAATAGGCTTTAG
 GCATCTCTAATTTTAAAAAATTTATTCAGGCTACTTGGATGCACAAAAGAGTTGAGACCT
 ACTGTCCTAGAATCATAGAATTTTAAATGACGATAGAGACCTTAAGCATCTAGGTGCTTTC
 TGTACTTTTACATGTAAGGAACTGGCATTCTAGGCCAGTACCATTGCCATGCAGCTAA
 TTTGCCCTCTTGTCTATAGCTCACTCTGCATCACCCAACCTACCGTTCTCACTGTTTCTT
 CTATAACCAATCTCCTTCCCACTTCTGTTCTTACTCATGCCATTCTTCCCTCAGTCAT
 TTTTCTTCTTCCATACAAATCCATGTCTTTAAAAAGGAATAATCCTACCTCCTCCACA

FIGURE 14.1

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TAGCTTTCCAATTCTCTGTTGCCACATTTGTCTCCCTTTCAATACTTCTCTGTTGTGTT
 ATGTGACACATCACATTTGATATACTCTGTACTGTGTTTCAAGTATTGTATTCTCTGTT
 TACTCAAGTCATTATTTTCAAGTACTGACTACCCAGTAGATGCTTTAAGTCAGGATTTCTCA
 ACCTTGGCACTGTTGACATTTTGTAGCTGGATAATTTTGTGTTTGGGGGCTCTCCTGTAC
 ATTTTAAAGATGTTTAAACAGCACCTTGGCCTCTATCCAGTAGACGCCTGTACTGCCTCCC
 CCTATCTGTGACAACCAAAAAGGTCTTCAGACATTGTCTAGATGTCTACTGAAGGACAAAA
 TCACCTCTGGTTGAGAACCACCGCTTCAACTAAGTTATCTTCTCTGTACTCAGAACTTGA
 TGTGATTGCAGCAGGGGGAGAGGATTATATACACAGTGAATGCAAACGAACCTAAATCA
 CCATTCCGATATGGCCACACAATTTTCATTTCCCTTGTGTTAGCAAGAGATACCCTAGGC
 TTTGGACCTGATTATTCCTAAGGCATTCTGATGTATGGTTTACCTGCAGATTTCTGGT
 AATACTGATACCTCAGTTTGGGTCAAAGAAGGTCAATTAATTGATTGATTGATTGACT
 CCTGGAAGACGCTCCTTTCTAGCTGTCTCTTTCTCTTTACCTGAATAGCCAGGGC
 TCTGTGGTTCAAGTGAAGTATTTTACATAAAAAATTAAGTGAACATTGGTCTGCAGAG
 TTTGCTCAATATAACTGAGCACATATTGTGGCTTTATGGAGCTGTTACTACTTTTTGAC
 CAAATAAATAATTAGAAGTATTTTCTCCTCAATAAGGTTCAATTTTCTTTTTTTCAGT
 GAGCTGGTAGAGTTTCTTTTTTGTATTTTCAAGGCTCTTTCATATTTCCATCTCTTAA
 GTTTCTTTCATATGAAGTAGAATTTATCTGGATTATGTATTGCTGACTCTGATGAAACCC
 ATAGAAAGCATCTGGGGCTTGATCACCTTCATTCTTGTAAATAGCTCACACGGTTACAGCT
 GATATGGTAACTTAAGACTTTTGTATTCCAAATCTAGGCAAAATACACTCAGTTGAAAGAA
 TTTGTGAGCCAGAACAGTTGGACTGTTCTGTGAAATTTGTGAGAAAAATTACACAATAA
 GTGATACATGATGATGGCTTTCTAAATATAAAATTTGTAATAACATGGTTAATTTCCAGT
 ACGTTATATTGTCCAGAGTGGCTCCAACATTGTTTGAATTTGTCTCATTTAAAGAAA
 CATAAGCTGGCTATGGTGGCTCAGCCTGTAATCCAGCACTTTGGGAGGCTGAGGCAGG
 CAGATCACCTGAGGTGAGGAGTTCGAGACCAGCCTGGCCAAATGGTAAAACCCCATCTC
 TACTAAAAATACAAAAATTAGCCGGGCATTTGGTGGGGGCTGTAATCCAGCTACTTGG
 GAGGCTGAGGCAGGAGAATTGCTTGAATCTGGGAGGTGGAGGTTGCAGTGAGCCGAGATT
 GTGCCACTGCCCTCCAGCCTGGGTGACAGAGTGAGTCTCCGTCTCAAGAAAAAAAAAAAA
 AAAAGCAAGAAACATAAAGACTGGGCATGTTGGCTCATGCCCTGTAATCCAGCACTTTGA
 GAGACTGAGGTGGGAAGATCACTTGAGCCCAGGAGGTTAAGGCTGCAGTGAGCCGTGATT
 TTGCCACTGTACTCGAGCCTGGGCAACACAGTGAGATCCTGTCTCAGGAAAAAAAAAATT
 GCATGTAAATGAATGAATTTGATATTTAATATTTTAAATTATGAAAACCTGTTCTGTAGAG
 ATGTAGATCTTGCCATGTTGCCAGGCTGGCTTTGAACCTTCTGGGCTCAAACAATCCTCC
 TGTCTCAGTCTCCCAAGTATAAAGATTACACATGTGAGCCACTGCACCTGGCCTAATAT
 TTTTAACTTAATGAATTTTATTTTATATATAAATAAATTAATAACACTGAAGCTTCTGATA
 TAATAAGTCTTTTTTGTGTGTGTGACGGGTTCTCACTCTGTTGCCAGACTGGAGTGTAAT
 GGCATATCATGGCTCACTGTAGCCTCAACCTCCCTGACTCAAGTGATCCTCCACCTCG
 GCTTCTGAGTAGATGGGACCACAGGCGTATGCCACCACACCTGGCTGATTTTTAAAT
 TATTATTGATACATATTAATAAAATTTATTTTATTTTAAAAATGATATATGTGGCTGGGC
 ATGGTGGCTCATGCCTGTAATCCCGACAGTTTGGGAGGCCGAGGTGGGAGGATCACTTGA
 GACCAGGAGCTTAAGACCAGCCTAAGCAACATAGTGAGATCCCATCTCTATAGAAAAAAA
 AAATGGCTAGGTGTGGTGGTGTATGCCTATATTCCAGCTACTCAGGAGACTGAGGTGAG
 AGGATTGCTAGAGCCAGGAGTTTCAAGTTACAGTGACCTATGATTGTGCCAGTGCACTC
 CAGCCTGGGCAACAGAGCAAAATCCTGTCTCAAAAAAAAAAAAAAGTTGCAAAATGCTTAT
 GATGCAATATAAGTAGTGGAAAAGGATATTAATTTGTGCCTATATGAACACAACCTATATG
 AAAAACTTGACATAGAGAAAAGGATTAACAAGAAATAGACCAAATTTGTTACATGGTTG
 TCTTGTGTTGTGGAGAGAATATCAGTAGTTTCATTTGTTTCTTCCAGTTTATATGTTTTT
 CGAGGTCTCTATAATGAGTTTGTAAATGTTTAAATCATAGAAAACCTTTTTTGGTCCTTG
 GCCACAACTTACATGTTTTAATGTAATGCTTTTTTAAATGAGAATAAATGTTATATTTT
 GCTTTTTTAAACCTATATTCCCATAGTTATATGAGCCCTTACAATTATTAAGAGGCTGC
 ATAATATAACGTTTCTGGAAGGTTACAGAAGAAACAGCAGTAATTACCTCTGAGAACAGA
 GACATGGCTTCACATTTTACCCTTTTGTACGTTTGTGCTTTTGGCACATGCATTTATTA
 TTCTTCCAATAAATAAGTAAATAATATGGATTGTATACTCCATCTGGTTGGTGTTCAT
 AATCTAAAAATTATATTGCTACATTTTTTAAAGATGATATGTGTTTCTACTTATTAACGTA

FIGURE 14.2

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TATGTTAAATAGTAAATTTATATCTTATTTAATAATTTCCCTATTGATAGACATTTAAG
ACAGTCTCAAGTGTTCACTATCATAGAAAATACTGCACAGATAGCTTTTGCTATAGTTTC
TTTTTCTTTGAATCGTTAATTGGGAATAAATGCTCAAATAGTTATATGTGGCTCAACTG
CTATTTAAGTTTATTGACTGACTGCTGCCATTTTGAATTCTGAAGGGTTGATTAAATTT
ATAATGCTGCCATAAGAATATAAGGGTATTGGCTTCATTAGCATCCACCAGCATTGGGTG
TTGGAAATGATTATAGATTTTAAATGCTACAACAAATGTAGATAACAGAGAACTATCTA
TAGAACTCTTTTGGACATGTGAATTGTAATAATAGTTTATTTTCATGTGAATCCAGAAA
AATGTATACGAAAACCTTTTTTCTCTCATTTCTTATATGAATAGAAATCAAGCTATAGAA
GTGGTCTGGAGTCACCAGCCTGCATTCTTGAGCTGGGTGGAAGGCAGGCATTTTAGTGAT
GGGGACAGGTAAGCACATGTGATGGCAATAACTTTCTTCTAATATCACATAATATAGCA
ATAGAAATAAAATTTAAAGTTTAGATTTTTTGTAAAGGAGGTGAGATGTCACCTAATTT
GTATGCTATTATGTAAGTAGTCTAGGATATTGAAGCTGACTATACTCTGTTTTTAGGTCA
TTATCTTGTAGTTTACCATACTCCCTACTTGCTTCTTATTCTACTATTTAACTCATTTTC
CACATCCCCTAATTTTGGTTTCATGAAATATTTTTTCTTCTGAATTAAGTTTCTACT
TACTATTATTAACTTTATTTCTGCATATTTTATAACCTTCCATGGTCTCACTTGATTA
AAAATAAAAAATTCAGCTGGGTGCGGTGGCTCACACCTATAATCCCAGCACTTTGGGAGG
CCAAGGTGGGCGGATAATTTGAGGTCAGGAGTTGGAGACCAGCCTGCCAACGTGGTGAA
ACCCCCCTCTCTACTAAAAATTCAAAAATTAGCTGGGCATGGTGGCAGGTGCCTGTAAT
CCCAGCTACTCAGGAGGCTGAGGCAGGAGAATTGCTTGAACCTGGGAGGTGGAGGTGCA
GTGAGCTGAGATTGCACTGCTGCACTTCAGCTGGGTGACAAGAGCGAAACAATGTCTTGA
AAAAAATAAAAAATAAAAAATTCACAACACAGGGTTATTATTTTTCCATTTTGTGTTT
CCCTTATGAGTTTAAATATGTTTAGATTATAAACCTGAAAGCTTGAATACCTATGTCTATC
TTTTGTTTTCTTATGTTTATCAAGTTTATCTCTTAAACATTTTCTAACTGTAAGAATAA
TGTGAGGCTGGGCTCAATGGCTTATGCCTGTAATCCCAGTGCTTTGGGAGGCCAAGGTGG
GAGGACCCTTGAGGCCACGAGTTCAAGATTAGCCTGGCTAGGCAACATAGCAAGACCCT
ATCTCTATAAAAAAATTAaaaaaATTAGCTGGGCATGGTAGCAAATGCTTGTAGTCCCAG
CTACTCAGCAGACTGAGGTAGGAGGAATGCTTGAAGACCAGGAATTTGAGTGACCTATGAT
TATGCACTCCAGCCCGGGCAATAGCAAGACCCTATCTCTTAAAGAAGAAGATGTAGTAA
TAATACATATTCTATTATACTATTTTACCATTGAAAGTAAAAATGAGTTTTTACCTTTT
CCCAGTCCCATCCTCAGAAATGGGGATCTCAGTAGACCTTTAGGATTGGAAGAATGAGATC
ATTCTATTTTTCTGCAATTATTACCCACAAAATATTTTCAATACCTTTCCATGTATTAC
AAACAATGTGCATTTAACATGCTCTCTCTCTCTCTCTCTCTGTGTGCGTCTTCATGA
TCCTCTGTTGCGCCCTGCCAGTAAGACACTATCTCTGAAGAATCACTGATAGGAACAG
AAAGTGGACTGGCTAGGCCAGGAGTCCCTAGCTTCTTAGGGGGCAGGAGCTGCTTTGTGC
TTTCTCAGAATCAGATATATATGTGGACTGAAACATTTAAAAACAGAATAGCCAAGGGTG
CTATACGTTTAAACTTATATAGATGGGGCTACATTGCTCTCTATTACTAATTTCCCATG
ACAATACACGAGAGTGCCATGTCTTTTAACTTGTTTTGAGCACAGACTAATCTTGTTTA
TGCATGTTTTTTGATGAGAATAGGCTACTCATGAGAAATCTGTAAACCTAACACTAGTCC
CTTGCACTACTCTAAATTGTTGCTAGAATCTTAAATTTTAGCACCAGACGGACCTTAGAA
ATCATTAACCTTTGGTGCTTTGTTCTACAATAACAAGGAGATGGAATATTTTACCCAGGATT
GCTTAGCAGGTTACAGTTCTGCCCTCTGAGTACCCAGCACTTCCCTGTGGGCAACATCAA
CTTCTGATTTTCAAGTCTTAATTAGTACTCTGAAGAATCCTACTTGTTTTTAACTCCCA
TTTGCTTTGAAGTGACTTTACCTGATTTTTTTTAGATCCCTTATTGCAGCAATGCCACTAA
GAAACTGAGTCTCTAGCTTCTTGGTGGGCAGGAGCTGCTTTGTGCTTGCTCAGAATCATC
CTTTTCAGTAAGGGAGATATTGAAGAGAAATCTACTGAGGAGTCTGGGGGTGAGGCACTC
AGGGAAATCCTGCTCCAGTCCACAAAAGCAGAGAGGAAGGGTTGGTTACCTAGACTATTT
AACATGCAGAGGCTTTGGATTTTACTCCTTTAATCCTTGGAATGCCTATGGAAGGGGAA
AGGAAGTAAGATGGTGAAGTCCAGCTTATAGACATACTAGTGTTACATATATTTAACTAT
AATAGGAGGGTATTATTAGTTTTACTTAACTTTCAACTGTGAAGGATTATACCTCTCAAT
ATTTGTCTCCAGTGTCTATTTTCACTTTTCTTGAAGCAGCATGTCTGTT
GCAAAACTTCTAGAAATAATGAGAATATTTATATATTAGATCAAGCCATAACTTGATGAT
ATAGTCATTTCTTCTTATATTTTTTACTTACATTTTACATTTTAAATGATTACTTTTCAAT
TTTGAAAAACATGTCATGCTGAGATGTATTTTCTTCACTTCTGTAATTAGTTATGAAACA

FIGURE 14.3

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GT TTTTCTCTAAAATGCTGAGTATATCAAGTCTTGGCTAAGAATAAGTAATAAAATATTTGC
CACATGAAAGACTACACATATAGCCAGGTGCAGTGGCTTGACCTGTTTTCCAGCTACC
CAGGAGGCTGAGGCAGGAGGATTGCTTGAGCCCAGGGTTCCAGGCTGCAGTGAACATATG
ATTGTACCACTCTACTCCAGAATGGGTGACAGAGCCAGGCCCCATCTCTCAAAACAGAAA
AGAAAGATTACATAGACTACATATACACCCCATCCAAAACATACACACATCTACTTA
ACCTAAAATGGTAAGAAGATAAATTCTTATTTTCTAATATATGACACAGAAAAGTTTTTT
TAAAGTAGTTTTAAATTTTTAATTTTTTCTAGGTATTTCTCAAGCCATGTTCCCATGTGG
TATCTTGTCAACAAGTTGAGGTGGAACCCCTCTCAGCAGATGATTGGGAGATACTGGTAA
AGAAAACCAAATAAGAAGTATCTCATTAAAGGTTAAATTACTTCACAATATCAATGTCTT
TAGCTTTCTCTAAGCTTTATTATATATTCTGAGTTGGTTTTGAATTATAAGAATGAATTG
GGGCCAGGCACAGTAGCTCATGCTTATAGTCCCAGCACTTTGGGAGGCCAAGGCAGGTGG
ATTGCTTGAGTCCAGGAGTTCAAGACCAGGCTGGGCAACATGGTGAAACCCCGTATCTAC
TAAAAATACAAAATTAGCCAGGCATGGTAGTGCATGCCATTAGTCCCAGTCACTTGGGA
GGCTGAGGCAGGAGAATCGCTTGAGCCCGTAAAGTCAAGGCTGCAGTGAGTCAGGATCTT
GCCATTGTACTCCAGTCTGGAACACAGAGTGAGACCTTGTCTCAATAAAAAAAGAATGA
ATTGATAGAGATCTAATGTACAACTGACAACCTATAGGTAAATAAAATTGTATTGGGGATT
CATGTTAAATGAGTAGATTTTTAACTACTCTTACCACAAAAACACAAAAGTGGGTAACGT
GAGATGATGTATATGTTAATTTACTTCTACTATAGTAACCATTATACTATCTATATGTAGC
TCATAACACCATGTGCTGTATATTAATATGCACATTAAATTTGTTTTTTAAAAAAGA
ATTGAGATTTTTTTTTAACTAGATATGGAGTGACAAAATGTAAAGTGAATTGATCTTTTC
GTCTGTTGGTTCTAGGAGCTGCATGCTGTTTCCCTTGAACAACATCTTCTAGATCAAATT
CGAATAGTTTTTCCAAAAGCCATTTTTCTCTGTTGGGTTGATCAACAAACGTACATATTT
ATCCAAATTGGTAGGTGCTATTGTAAATTTTGCTGTCAATTCTACACTATAGCATTGAG
TCCAAAGTAGAAATGAATGTGCACTAATGAGCTTTATTTTCTACACAGTTGCACTAATAC
CAGCTGCCTCTTATGGAAGGCTGGAACCTGACACCAAACCTCCTTATTCAGCCAAAGACAC
GCCGAGCCAAAGAGAATACATTTTCAAAGCTGATGCTGAATATAAAAACTTCATAGTT
ATGGAAGAGACCAGAAAGGAATGATGAAAGAACTTCAAACCAAGCAACTTCAGTCAAATA
CTGTGGGAATCACTGAATCTAATGAAAACGAGTCAGAGATTCCAGTTGACTCATCATCAG
TAGCAAGTTTTATGGACTATGATAGGAAGCATTTTTTTCTTTCAATCTGAGAAGAAACAAG
AGACATCTTGGGGTTTTAACTGAAATCAATGCATTCAAAAATATGCAGTCAAAGGTTGTTT
CTCTAGACAATATTTTTCAGAGTATGCAAACTCTCAACCTCCTAGTATATATAACGCGTCAG
CAACCTCTGTTTTTTCATAAACTGTGCCATTCTATGATTTTCCATGGGACCAGGAATATT
TTGATGTAGAGCCAGCTTTACTGTGACATATGGAAGCTAGTTAAGCTACTTTCTCCAA
AGCAACAGCAAAGATAAAACAAAACAAAATGTGTTATCACCTGAAAAAGAGAAGCAGATGT
CAGAGCCACTAGATCAAAAAAAAATTAGGTGAGATCATAATGAAGAAGATGAGAAGGCCT
GTGTGCTACAAGTAGTCTGGAATGGACTTGAAGAATTGAACAATGCCATCAAATATACCA
AAAATGTAGAAGTTCTCCATCTTGGGAAAGTCTGGGTTAGTATAAATTTTATAACTTGGG
AGAAATTTTATGTGGCTTAAACATCCCCAAATTATGAATTAGAATAGTATTTTCATATATA
AATTGAAAATCAATTAAAAAGAAACACAGTGCCTAAAGGCACTTGGGGGACACATTTACG
CTTTGCAGTAAAGTCCTTGTGTTGGATAAAGATTGTATGTTTTCTGGCCAAGTAAGCTTGA
ATAGGTACAAGCTTAGATAGGTTTCAAGCCAGAGAGGTCAAATTAAGTGCCTGAGATTGC
ATAGCTAGTGTTACAACCTAGGATTCAAACCCAGGCAGATTGACTTGGGGGTTTCATCAGGA
TGGAGTGCCCTACAAAGCCTCCCATCTTTAATGCTTGCAGATTTGTTCCCGATGAGGT
AAGCAACTTGTTAATATTAGGGAAAAGGGCCAGGTGTAGGGAGAGATCCATGGCATGAGGT
AACCTTCTGCTGCATGTGGTGGCACCTGGATTGGAATGCATCCAGGAGCTGCTTACCCT
GCCGGTGTCTGCTCTTTAATTTGTGTATAACGGAGAGGAAGTAGACAGGGCAACTAGTGC
TCCAGCCCCTCATCCTGGCCACAAATATTAATGCTACCTTTATATGACATAAGTCACTAG
TCCATTTATTGGAACCTAAATTTGAACCACTGTAAAGTAAGACTTCATAGTGATAAAGAG
AGGAACCTGTGTTAGGAAAGAGAATAAAATAGAAAGAGAAGGTTGTCTCCTTTTGTAGATTT
TTTTTTTTCTCCAACAGTTTTACCTGTGACCTTTATACAAATAACTGACAAAGCATTAA
TCTCTTTGGCCTACATCATTTTCTTTCTATTTTTTTTTTCCACAAGATGGAGTTTCACT
CTTCTTGGCCAAGCTGGAGTGCAGTGGCATGATCTGGCTCACTGCAACCTCCGCCTCCCA

FIGURE 14.4

FIGURE 14.5

Figure 1 consists of 26 panels (a-z) showing maps of the tropical Pacific region (20°N to 20°S, 180° to 10°E). The maps display precipitation anomalies for the 1998-1999 season, with shaded areas indicating significant differences. The panels are arranged in a grid, with the first row containing panels (a) through (f), the second row (g) through (l), the third row (m) through (p), the fourth row (q) through (r), the fifth row (s) through (t), the sixth row (u) through (v), the seventh row (w) through (x), the eighth row (y) through (z), and the ninth row (aa) through (ab). Each panel includes a title and a legend. The titles are: (a) 1998-1999, (b) 1998-1999, (c) 1998-1999, (d) 1998-1999, (e) 1998-1999, (f) 1998-1999, (g) 1998-1999, (h) 1998-1999, (i) 1998-1999, (j) 1998-1999, (k) 1998-1999, (l) 1998-1999, (m) 1998-1999, (n) 1998-1999, (o) 1998-1999, (p) 1998-1999, (q) 1998-1999, (r) 1998-1999, (s) 1998-1999, (t) 1998-1999, (u) 1998-1999, (v) 1998-1999, (w) 1998-1999, (x) 1998-1999, (y) 1998-1999, (z) 1998-1999, (aa) 1998-1999, (ab) 1998-1999. The legends are: (a) 1998-1999, (b) 1998-1999, (c) 1998-1999, (d) 1998-1999, (e) 1998-1999, (f) 1998-1999, (g) 1998-1999, (h) 1998-1999, (i) 1998-1999, (j) 1998-1999, (k) 1998-1999, (l) 1998-1999, (m) 1998-1999, (n) 1998-1999, (o) 1998-1999, (p) 1998-1999, (q) 1998-1999, (r) 1998-1999, (s) 1998-1999, (t) 1998-1999, (u) 1998-1999, (v) 1998-1999, (w) 1998-1999, (x) 1998-1999, (y) 1998-1999, (z) 1998-1999, (aa) 1998-1999, (ab) 1998-1999.

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TTTTGGCTGCTGTGAATAATGCTACAGTGAACATTGGTGTACAAGTATCTGTTTGAGTTC
CTCTTTTCAGCTCCTTTGGGATATACCTAGGAATTATGTTTAACTTTTGGAGAAGCTGAG
AAATCTTTAATAAATGATAACACAAATACTTATATTTGCCAATGCAAATATGAATATTTT
TGGCTTTTAAGAGATTGATCATTTTGCCACGTGGTTGTAATAAAAAAATTGTCCCATG
TTGTTTCAGTATTAATATTGTAGCCTAAAAGAGTGCTAGACTGTTTACTTTTACTCAG
TTAATCTTTGGATACTGGTAGAGTCAGGAAATGAGATATTGAACTTAAAGATCTTTGCA
GGTGGGGTCCAGTGGCTCACACCTGTAATCCTAGCACTTTGGGAAGCTGAGGTGGGAGGA
TTGCTTGAGGCCAAGAGTTTGAAGAATAGCCTGGGCAACATAGCAAGACCCCATCTCTACA
AAAAAATTAAAAAATAAAGCCAGGCGTGGTAGCTCACGCCTGTTATCCCAACACTT
CGGGAGGCTGAGATGGGTGGATCACTTGAGGTGAGGAGTTGGAGACCAGCCTGGCCAACA
TGGTGAAACCCCATCTCTACTAAAAATACCAAATTTATCGGGGCGTGGTGCTAATCCTGT
AATCTCAGCTACTCAGGAGGCTGAGGCAGGAGAACCCTTGAAGTGGAGGTTGGAAGTT
GCAGTGAGCCTAGATCTCACCCTGCACTCCAGCCTGGGTAAACAGAGCGAGACTCTATTT
CAAAAAAGTAAAAATAAAAAATTAGACACATGTGGTGGCACATGCCTGTAGTCTTAGCTA
CTCAGGAGGCTGACTGAAGTGGGAGGATCTCTTGAGCCCAGGAGTTCCACACTGCAGTGA
GCTATGATTGTGCCACTGCACTCCAGCCTAGGCAATATCTCAAAAAAATTTTTTAAAT
AGATTATTAGGCCAGAGCTGGTGGCTCATGCCAGTAATCCCAGCACTTTGGAAGGCCAAG
GCAGTCCGGATCACCTGAGGCCAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCC
ATGCTCTACCAAAAAATACAAAAATTAGCTGCAATGTCTATAATCCCAGCTACTTGGGAGCC
TGAGGCAAGCGAATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGTGGAGACTGCGCC
ACTGCACTCCAGCCTGGGCGATACAGCGAGATTCTGTCTCAAAGAAAAAGGAATTTGTTT
TCCTGTCTTTATCGTAGAGGGAGGAAAGGGAGAATGGGGTTGGAATGGTTATTGAGTGAG
CCACATTATGGTAGATGTATCACTGGGCATAGAGAAAAGGAGCATTAAAACTTTCCGC
CTAACAGATGTTTCTTCAGGCTACACTGCACTCATTGTGCTAACTGTAATGTCAAATCCC
AGACCTGTGCCTATAGAACATGAACATCCTTCATTGGATTGTTTGGTCAGGCTTACACT
TTATTAGGAAGATCAGATGTTAAAATAAGGGTGTAAAGTTAAGTTCAGATATGAGGATA
ATTCACTACTATTCTTTTCTGGCAGCCTAAAGACATAAGTGAAGAAGACATAAAAACT
GTATTTTATTTCATGGCTACAGCAGTCTACTACCACCATGCTTCCTTTGGTAATATCAGAG
GAAGAATTTATTAAAGCTGGAACTAAAGATGGTGAGTACATTTGTTATTTTGACTTTTTT
TTCTATTTAAATAGTTGTACATTTTAAATTGTTCTTGCAACCTGTCATACCTGTGAACAG
TATGTGAATAGTGAAATATAATTATGATAATTAACAGTAGTTTTTATGTATTGAAAAAT
ATCTTTGGCCGGGTGCAGTGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCA
GGCGGATCACTTGAGGCCAGGAGTTCGAGAGCAGCCTGCCAACATGGCGCAACCCTATCT
ATACAAAAAATACAAAAATTAGCCTGACATAGTGGTGTATGCCTGTAGTCCCAGCTACT
TGGGAGGCTGAGGCAGAGGATCACTTGAGCCCAGGAGGCTGTGTGTTCCCTGCCACTGCAC
TCCAGCCTGGGCAGCAGAGTGAGACCCTGTTGGGGGAAAAAAGTCTTTAACTT
AAATAAATTTGACATTTAAATCCTTAAATTATTTTCTCTCTGTTTCAGTACTAACTCTGC
ATTTATTACTTTCTTTTAAATAGGACTGAAGGAATTTTCTCTGAGTATAGTTCAATCTTG
GGAAAAAGAAAAAGATAAAAAATTTTTTCTGTTGAGTCCCAATTTGCTGCAGAAGACTAC
AATACAAAGTAATAGCATGTTATTGAATATTTAATAAAATACTATTTGTTACATATGATTG
ATAATAAAGTATGAAGTTCCTTGTAACACCTTGCATTGTGAAGTGTATTAAAAACCTGCT
AAGAGTAAGGAATAACTTGATTTAAATATTTTATTCTGTAATCTCTTTAAATTATCTGT
ACAAATTATTGACTTAACCTAAATTTAAAAATGAATGCCTTAGCACAATTAAGTTCCAAG
AATAGAGTTGATCATGTTAACTGGTAAATGGATCATGATTTAAATTCCTCTAGGATTGA
AACAAATGAAAACGTAGTTTTAAGGGTTTGATTTTTTAAATTCCTATTTTACATGCAAT
TTTACTGCACAACCCATCTTATTTTGACAGTTCCTTAAATTCGCAACTCTTCAGAAATATT
ATCAGATCACTTTTCTTTGCTTCCATAAGTTTTTTTATTATTATATTATTTTTTTTTT
TTTAAAGACGGTGTCTCACTTTGTGCGCCAGGCTGGAGTGCAAGTGGCATGATCATGGCT
CACTGCAGCCTCGACCTCCCAGGCTCAGGTGATTCTCCACCTCAGCCTCCCAAGTAGCT
GGGACCACAGGCGAATGCCATGATGCCTGGCTAATTTTTGTATGTTTTGTAGAGATAGGG
TTTACCATGTTGCCAGAAATGTCTTGAACCTCCTGGGTTCAAGCAGTTGTTCTGCCTTG
CCCACCCAAAGTTGTGGGATTACAAGTGTGAGCCACTGCGCCAGCTATTCTAGAAGTAT

FIGURE 14.6

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TTTAAGAGTCATCTTTTTTTTTTTTTTTGAGATGGAGTCTCACTCTGTCACCCAGGCTGGA
GTGCAGTGGCACACTCTCGGCTCACTGCAACCTCCACCTCCTGGGTTCAAGTGATTCTCC
TGCCTCAGCTTCCCTAGTAGCTAGGATTACAGGCGCATGCCACCATGCCCTGCTATTTTT
TGTAGTTTTAGTAGAGACGAGATTTACCATGTTGGCCAGGCTGCTCTTGAACCTCTGAC
CTCAAGTGATCTGCCCTCCTCAGCCTCCCAAAGTGCTGGGATTCTAAGTGTAACCACCA
CACCCAGCCAAGAGTGGTCTTTTTTACAATATTATTTTTTTGATTAGGACATTCTTCTGT
CATAAAATTGAAGATACTCTAGTCATTTAGAATTTTCATTGTTTTTGGAACTAGACATTGTT
TCTTTATTTTTTGAATGTTATTGAAGGAATACCATTGGGAGAAGATACAAATGTAAGAAT
TGTGAAAAGGATAATTGTGACACAAATCAAAATTATAGATAAAAAATATACCTGTAAAATG
TATTAAGGCAATAACATTCTTTCTGCTTGTTGACCATAAATATTTATATTCCTTGGATGG
GTACATTGTTATTGTCAAGGGTGTAAATAATGATCTTGCATGCATAATTTATTCTCTC
TGGTATAACAGAATCAGCAATTTAGTTTTCTGGGACCCGAGAAAAACATGCAAAAAGACAT
ACTTTGAATGTAAACTGATTTTTCTTGCAACTGTAGGTCCTTCTAGATCCTATGGTA
AAAGAAGAAAACAGTGAGGAAATTGACTTTATTCTTCTTTTTTAAAGCTGAGCTCTTTG
GGTAAGAAGTTATGGCCAACTAGCATGTTAGACATGTTTTTAACACTATATCTGGCAG
AGTTTTCAATGTAAATATTAAAGTAGATGTTAATGTCAATAAGTGATCTTAATAATGCAT
CAGTAGATATTTTTTCAAGGATGTCTCTATCTTCACGCCTAGCTTATAAATTGCTTGT
CGTCTTTTTTTTTTCTCTTTATTTTTATGTTTTATCCATCCCTGGTGGTAGGGGATAA
CCTTGTCTTCTCGATAACAAGAAGTCTGAAGCTTATTAGAAATTTTACTTTGAGAATTG
ATCGATGAGAAGAAAGCAACTAGATATCACGTGGATCATATATGCTTGAATAAAAAAATA
ATTCTTAGAACAAATAAATACATTTTAAAGTTAAAGCCAAAAACATTAGTTGAATGTTT
AAAAATATTTCAAATTAAGTTATTCCTTCACTGTCTTGTATTACTGTAATAATTTGGATT
ATTTGTGTTTTTCTCACTTTTAAACAAATATTTAAAAAATTCCTCTTTTGATTAAAGTA
GGGCTAGATAAAATATAAAAAATATTTTTTAACTCCTCTTAATTTCCATATTTCTTATA
TAATATGAGAATCTCTTATAAACAACCTCCTTAGAAGTCTCCACAGAAGCTTTGGTAGA
TGTAGTAGTAGGGATTGATTTCTTAGAATGGTATAATCTGTAAATGTTTTAGTAAAGG
ATTAAACGATAAAGTCAAAATGTTTATAGCACAGTGTATTATAATAAAAAATAAATCTC
TTTTTTTTTTTTTGGAGATGGACTCTCACTTTGTCACTCAGGCTGGAGTGCAGTGTTGCAA
TCTCAGCTCATTGCAACCTCCGCCTCCTGGGTTCAAGCAATCCTTCCGCATCAGCCTCCT
AAGTAGCTGGGATTACAAGCATGCACCACCACACCTGCCTAATTTTTTGTATTTTTAGTA
GAGATGGGGTTTACCATGTTGGCCAGGCTGGTCTCAAGTGATCCGCCTGCCTCAGCCTC
CCAAAGTGCTGGGATTACAGGCGTGAACCACTGTGCCAGCATAAAGTAAAAATCTCTTCA
GACTCTCATGTGATCATGTAAAGTGGCAGGCAGTCACAGTCAAGAAGTAGTTTAAAGTTC
ATGTTTGTATAAATATAATCTACAGATTGATACTGGATTTCATAGGTAATGTTTAAAGAGAA
AATAAGTTTTTTAGTTATCCTCAGTACTTCAAAAGCACCCATTTATGATTATGTTGATTAC
TAAACTAAATCATTTGGGGGCTAGAGGTGTTTTTTTTATGTGTTAAGATTCTTTAAGGAGT
TCTATTAGGGCAAAACTTTTAGTAACTGCATATTTTAAAGTAATAAAAACTAATTTTAAA
AGCTTGGAGGCTGGGCGCGGTGGCTCACACCTGTAATTCAGCACTTTGGGAGGCCAAGG
CGGGTGGATCACTTGAGGTGAGGAGTTTGAACGAGCCTGAGCAACATGGTGAAACCTTG
TCTCTACTAAAAATACAGAAATTAGCCAGGTGTGGTGGTGGGCACCTGTAATCCCAGCTA
CTCGGGAGGCTAAGGCAGGAGAATTGCTCGAACTTGGGAGGCAGAGGTTGCAGTGAGCCG
AGATCATGCCACTGCCTCCAGCCTGGGTGACAGAGCAAGACTCCGTCTCAAAAAAAAAA
AAAAAAAAAAGCTTGAAGTCAGATTGCACATTAATCAGTATACTTTCTCTCAAGTAGGGG
ACAATTTCTAAGATTTTAGTCTTTTAAATTTTATTAAGTAGTCTGAGCATGGTGGCTTGT
GTCTATAATCCCAGCACTTTGTGGGGCCGAGGCAGATGGATCACTTGAGCCAGGAGTTG
GAGACTAGCCTGGGCAACATGGCAAAACCCGCTCTTACAACAAATGCACACACAAAAAA
CCCAATCAGCTGGGTGTGGTGTTACACTCCTGAAGTCCCAGCTACTCGGGAGGCTGAGGC
AGGAGGATCACCTTTGCCAGGGCGTTTGAAGCTGCAGGGAGCTGGGTTACACCACTGCG
CTCCAGCCTGGATGACACAGCAAGCCCTTTCTCAAAAAAAAAAAGATAAAAAATTAAT
TAAATTAATTAAGTACACTGGGAAGGCAAAATTCAGCATTTTTTTATAGCTAAATTTAT
CCTGCTTCAGTCTTTTATCATGTAATATGTATATTTTTTACAGAGGAGTGAATTCCTTA
GCGGTATCCTCCTTGGAGCACATCACTCACAGCCTCCTGGGACGCCCTTTGTCTCGGCAG

FIGURE 14.7

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CTGATGTCTCTTGTTCAGGACTTAGGAATGGAGCTCTTTTACTCACAGGAGGAAAGGTA
 AGTGGTTAAGGTGTGTTTCATTTTCTGTAACATTTAATAACTTTTCATTTATCTTTCTTT
 GGGTTTTGACCATCTATTATATAGGGTGGGTTTTGACCATCTATTATATAGGGTTTATAC
 GACATATGGAAAGCATTCTTTTATCTACTAATATTTCTGTGTGTCTGCTTTTAGGTGTTG
 GGGGAGTGATGACGAATAAGACTGATGTTCTCCATGCCCTTTTCTGTGTCTGCTTTGATAC
 AATTATATGGTTTTTCTTTTATAGGCTATTAGGTGTTGATAGGGTTGAGTAACTTACAAA
 TGTTGAACCAGCCTTGCATACCTGTGATAAATACCACGTAGTTGTGGTGTATCATTCTTT
 CTACATTGCTGAGTTTTATCTGCTAATGTTCTGTTGAGCTTTTGTCCATTTAAGTTTGAA
 AGTGATTAGTTTGCAGTTTTCTGTTTTTGTGTTGTCTTTGTCTGGTTTTGCTATCCGTGT
 AAATCTGGCCTCATAAAATGAGATGGGAAGTATTCTCTCCTCTTCTTTGTTTTTTTGGGA
 AGAGGTTGTATAAAATTGAGGCTGAATCTTGGTGGTTGCCACAATGACAGGAACTATTTTC
 TGTGACTGAATATATTGGGAATTCCTATAAAGCAATTATTTTCTAGGGAAAGTGGAAAATC
AACTTTAGCCAAAGCAATCTGTAAAGAAGCATTGTGACAACTGGATGCCCATGTGGAGAG
AGTTGACTGTAAAGCTTTACGAGGTATGAGTATGGTAACACTCTATATAAAATCCCTTTTT
 CATTAGAAAGACAGGAATGTTATACATAATGCTGTCAATCTAATAAATACACATATCATC
 TAGTCTTTAACTTTTCTGTTTATCATTTAGTCATTAAATTTCTTTGGCTTTCTAATGTT
 TTTGATAAAATTTCTAAACTCTCCATATTTAATGGAGGCCTATTTTCTTAGCCAG
 AACTTTTTGTAGACTACATTTCTGGAAGTGCTCACTGACCACTCTGAAAAATTAGTAC
 TTAGAATATACCTCTAATTTGTTATAAATGATCTCTGAATTGCTATGAAAACTGGGAGAAT
 GGTTGCTTCAGGGGAGAGAAAGTAGGAGGCTGTGGACAGCAATGAGGAGAATTACAGTTC
 ACCATATAACACTTTTTGTACTTTTTAAAGTCCTTAACATTTACATTATTATCTATTCAATT
 AAAAAATATTGGGAAGATTTTACTTTGAACAGTTAATTTTTCCCCCATGGGTACCGCTGT
 CATATAGTTCCAACTAATCATGAACCTGTGTATTTCTGTTCTTTGTAAATTTAACTTTT
 GTAACCTACCAGGAAGTTTGAAGCCAAATTTGTGTTTCAAATATAGCAACTCCAGGATCT
 CTAGGCAGATGCATTTGCATTTGATTTTAAATGAATCTTGATCCCTTACTCTCACTTATG
 TTTTCCCACATCCTACTTTTTTATTTTGTGTAAGCCATCTAAAATCTCAATGGGATG
 AAAGTGGGTATAAATGAATACATGCATACAGGAATTATAGTAGCATATTCCTTTTCTTTT
 TTCTTTTTTTTTTTTTTTTGTAGACAGAGTCTTGCTCTGTAGCCCAGGCTGGAGTGCAGTGG
 TGCGATCTCGGCTCACTATAGCCTCCACCTCCCAGGTTCAAGCAATTCTCGTGCCTCAAC
 CTCCCAGTAATTGGGACTACAGGTGCATGCCACCACACCTGGCTAATTTTTGTATTTTT
 TAGTAGAGATGGGGTTTCCACCATGTTGGCCAGGCTGATCTCAAACCTCTGACCTCAAAGT
 GATCTGCCCTGCCCTTGGTTTCCCAAAGTGCTGGGATTACTAGCATAAGCCACTGCACCTGG
 CCTCCTTTTCTGAGTTTTATAAAATTTGATACTTTACTGCACGCTTTGAGACTGTATTAA
 TTGAACCATGTTGATGAACAAGTTTTTGTGATGGGTATATTAATAAAATATAGATCAAAT
 TTTTATAGTTAAATCAATATCGAGCTTTTCTAGTGCTTTCAAAGGACAACCTGAATTTT
 CCCAGCATGAAATGATACTGAAACCATTTCATATCTTCTGTATTAAAGGAAAAAGGCTTG
AAAACATACAAAAAACCTTAGAGGTGGCTTTCTCAGAGGCAGTGTGGATGCAGCCATCTG
TTGTCCTGCTGGATGACCTTGACCTCATTGCTGGACTGCCTGCTGTCCCGAACATGAGC
ACAGTCCTGATGCGGTGCAGAGCCAGCGCTTGCTCATGGTAAATGCATCCACCCTGGC
 TTAAGGTCTTGTTCTTTTGTGCTGAGCATTTTTTAGTCTTAACAATAAATCTACTCTCTT
 CAGAGAATAATATATGTGTTATGTTAAGTGTGTTGTTGAGGCCCTGATGGCATTCTAC
 AGTTGTCCTATAGACTGTAATAGCAAAATTGGTAGAGTAAAAACAGTGTGAAAATTCTGC
 AACTTCATGGTTAGTCTTTAGGGTTTTTCTATTCTCCCTTACTTATTGTTTAAATTTACAG
 ATTTACTCTTTTGTTCATTTGACAAATATTTGTCAAATGCTTGTGCACAGTCTGTATTCT
 CAAATTCAGGAGAAAAAGAGGGTGAACAGTATTAGCGCAGAACGATACTAATAATGAT
 GGCTACTGTGTATGATAGCCAGCCCTTTCTTGGCTTTCTTGGATTGCTTTGTATTCTAC
 ATGAAGATATTCCTGGGCTTTACAGGTCAATAAATGGAAATTCAGAGAGATTAATTTGA
 CCAGGGTGACCAACAAGGAGATGACAGCATACACTATGCGAGAAGTATACACAGAGTAGT
 GTAGGAGCATATAACCTAAACTGGGGGTGAGGTGGGATAAGGAGTTATCAGGGAAGGCTT
 TTTGGAGGAGTTGACAACTGAGCCGAGTTTTGATGGAAGAGTAGAAATTAGCATGAACCA
 ATTTTCATGCTAATAAAGAAGCAAAGGAAGCGTGGTCTACAGGCAAAAGCACAGAGGTACA
 GGAAGTAATGATATGTTGGGAATACCCTGTTGACTGGAGCTTAGAGTGCAAGGAGAGGA

FIGURE 14.8

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GTGCTAGGGAGGTGAGGTTGGAGGGTTTGGCAGCATTGACTTGCTTCAAGGTTCTTAAGA
GCTGAAATAGATATAAAATGCAACTAAGAGTGGCTTGGATTATTATTACCTAGTGTGTTA
ATCTCAAATTTTGAAATCTATAGCATCTATAGGACTGGTGTACTAATCTTACACTCGAT
CTGTTACTGTTCTTATACTAGATCTATTAGTCCAGTGTTTAAGGGAGTGGTGCAGATTTTC
TAGGTGAGGACAGGACTCAGATGTACATTATTAATGCCTATTTTCAGTTCTGACCTTCTCA
TATGAAACCTTATAAGACCTGGGGTAGGAAGAGATTGTTCTGGAAGTCATAGGAATATGA
ACTGTATTTTGTGTTAAACAACAATACAGTATGGAAATTTATCACCTTCCAGAATATTTA
TTTCAGAGACAAATTTTATCATTCGTTTCAATTTATTTTCATAAGATCCACGAGTAGGGAAC
CTCACTAGACATTGCTCTGAGTATATGGTCTGAGTTTGCAGTACCTCTTGTGTCTCCATT
AGATTTATTAGGTCCTCAATAGATAAATCAGGGAATAACTAGATGGATTCAATTTTTTAA
GACATGAAAGAGCGATACCATACATACTGCACCTTAAAGGTCAACCTTAGAGTATCATT
TTTTTAATGAATGTATAATTTTTAAATTTTCATGTTTACTTTTCCCTAAGCTTTTGCACAT
ATTGCTTAATTCAGCTTTGAATGATATGATAAAAGAGTTTATCTCCATGGGAAGTTTGG
TTGCACTGATTGCCACAAGTCAGTCTCAGCAATCTCTACATCCTTACTTGTCTGCTC
AAGGAGTTCACATATTTTCAGTGCCTCCAACACATTGAGCTCCTAATCAGGTAATACACT
ACTTGTAAGGATTATTGAATTATGTCCCTTTTATAGAAATTATTTTCAATTTTATTAGT
AATTCGTGGCTTTTAAATTTATGCTTCTCTTAATGATTTTAAAGGATATGTAAGTCAACATT
TGGTGCATATTGTGCTAGAGGCATCAAAATTATAATTTATAGCCACCTGAAATGTTAGTATG
CGCTTTCCAAGAAAATGACTTTTTTGAATAATGGTATTTCTTTGAATGAGAAAGAACAGAG
AGAAATAGATAGATGGCTTTTAAACACTTCATTAATTAACCTTTTTTTTTTCCACCATCAC
ATAATGGCACTTAGTCCCTTTTGGGAACCTCATGAGGGTTTATGTTAGTGTAGCTGAAAG
AAATATGTTCCAGGACTGGCAACATATTCTAAATCTTTAAATTTTACCTAGCATCT
ACCCTAAATATTGAGACCTGTGCTAGTTAACTGCTATTGAAGAACAAGGTATTATATC
TATTATTAAGGATAATAGAATGGTATTTGAGATATTGGTCATTGAATATGAATATGTTTT
GAGAAATAAGTTTTATAGGAACCAAAAAAATTCTTAAAGGAACCATATATTACTAAAA
ATGCTTCTTATTGGAGAAAGAAATGACAATCATTTATTAATGTGATTTTTTCACAACCTT
ATTAAGATATAATTTAAGTACAACAACTCACATAAAGTGTACAATTTGATCAGTTTTAA
CATATGTAGATGCCATGAAACCATCACCAATTAAGGAACAAACATTTTCATCACTCC
AGAAGTCTCCTAGCCCTTTTACTACCCATTCCCTCCCTGCTCCATCCCCAGACAACCTACC
AATTTGCTTTCTGTCACTATAGATTTGTCAACCTGATTTTCTCCAAATATACATTCAAAA
ATATACAGTTGAATACAATTGGAAATTCGAATTTTGTGTTTTTTCTTTAGGAACAAAGA
TGTGAAATTCGTGTGAATGTAATAAAAAATAAATTGGACTGTGATATAAACAAGTTCACC
GATCTTGACCTGCAGCATGTAGCTAAAGAACTGGCGGGTTTGTGGCTAGAGATTTTACA
GTACTGTGGATCGAGCCATACATTCTCGACTCTCTCGTCAGAGTATATCCACCAGAGAA
AGTATTGTTTTACTATTAACCTGAACCTTGAATCTTCTTTCTATTGTGGAGAAATGTAA
TTGTAGTAAGACAAGAAATTAAATATATTCCATTGTAGTATTGTAATAAGCAGTTATTTGA
GTAGAAAATTAGTGTTTTCCAGCTAAGATGATGGCATAATTTGAAAATTCATATAGTGAAT
ATAACTAGTAAAGAAGTTTTGTTTTATTTTTTAAACAGAATTAGTTTTTAACAACATTGGAC
TTCCAAAAGGCTCTCCGCGGATTTCTTCCTGCGTCTTTGCGAAGTGTCAACCTGCATAAA
CCTAGAGACCTGGGTTGGGACAAGATTGGTGGGTTACATGAAGTTAGGCAGATACTCATG
GATACTATCCAGTTACCTGCCAAGGTATGTTTAAAAAAGAAAAAGTGAATACTTACTCC
CAGAAGAACCCTGTATTATTGGCTTTGGCTTTATGTGTCAGCTTGCCCAATCTCCGTGT
GAGTCAACAAGTGTCTTACTGAGTTACCAATAAATGTCTTAACACTATTTTAGGTACTTT
AACAAATTTTAATTTTATTAATTAATTTTTTATTAGAATTGAGACCTCACTCTGTCTATCT
AGGCTGGAGTACACTCACAGCTCACTGCAACCTCAAACCTCCTGGGCTCAAGCAATCCTCC
TGCCTCAGCCTCCCCAGTAGCTAGAACTACAGGCATGAACCACCATGCCCCGCCAAGTCT
TTAATTTTCTTAGAGACGGAGTCTTGCTATGTTGCCAGGCAGACAGATTTTAAATGTGTA
TGATGCAGTCTTTGATGATAAGAACTTATAATGGAAAGCTGAGGTGATAGTTACAGTAA
ATACATTTTGATGTATAATTCTGTTTCTTAAATCATTCAAATTTAGTAAAGCAAGATG
AACTGTCTGCTGGGATTTGAGCAGAAATGGATAGGAATAAACTAGGAGGTAGAAGAGTTA
TCAAGGTTTACAGGACTGATGGGTGAAGCTAGATTTCCAGACCCGGGATGTCAGTCCTTG
AAAAGCAGACTTGGCAGGCATAGACGAGGCAGATAGCAGGATAAAGGAGACAAATGTAGA

FIGURE 14.9

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TTGTTCTTCAGAAGATCAGATGGTAGAGTCTAGGAGGTAGTGTGTTTTAATCAGAGATCT
GAGAGGCCAAAGATCATTGCGATGAGATCAGGGACCCATGCAAAGGAGTGAGAAAAAACT
GGGTTAAGGAGCCTGCTGCGATGGCAACTCCTGGGAACAGTGGCCACTGGGGCCTGGGACA
TGTTGATTGCAGCCAGGACTGTTAAAACAGTGTGAGAGAACATGGGTATGGAAGTACT
AGCTAGCAGGATCATGACCCCGATGCTGGGATGGGGCATCAAGCATTAGTACATGGAGAT
TCAGTACATCCAGATGCAGTACATGGAGACTATATGCGTAACTGCTGACTTTGGGCTTCT
TTCAGATTGGAGCAGAGGTAGAGGTGAGTGGGAATATTCTCAATAGAGGGAATAAATAG
GCATACCTAATAAAGGAGACCAGGATATTGCAGACAGTAGCCTCATGTTTGGCTCACCTG
TTCAAAAAGTTCTCTTGTCTTGTAGCAGTGGTGCCTTAAAAGGTAACCTTGAGAAGCAGTC
GATTATTTGTTTCAGCCTGGAGACTCTTGGGATATTTTACTATCTTTGATTGAATAGATTT
AAATGTACACAGCTCTCATAACTTGCCCCATGAAGCATATCCATGAAAGGCACTATACTT
GTTAAAAGATTGGTTTTGTACTTTTTTAAATGTAGTACTTTTTAATAAAAACAGGAAAAATAGA
AGTTCTGATGCAGTTATATGCATTTTATATAGAATGTGTTCTTAATTGGAAAAAATTTGT
CGTAGTTCCTTTGAGTTCATTTACAGTTTTTTAGTAGGAATTGTATTTTCTACTGTTGTAC
TTGCTGTTACTAAAGAAAGATGGTCTGTGATTACCATCTGAATTTTTTTTCTATACATTGA
TCTTTAGCTGCTACTTAGTCATTTCTGTTTAGACTTGAGCTCTTTTTCATATTTTTTTTT
TTTGTCTCTCAGTATCCAGAATTATTTGCAAACCTTGCCCATACGACAAAGAACAGGAATA
CTGTTGTATGGTCCGCCTGGAACAGGAAAAACCTTACTAGCTGGGGTAATTGCACGAGAG
AGTAGAATGAATTTTATAAGTGTCAAGGTATGTTGTCTACTTATCTTCTTTTTTTATTTA
GGTAAAATTAACATAAATGCAGTTAGCCATTTCAAAGTGTAATTCAGTGGCATTTAGTG
CAATCACAAATGCTATGCAACCACCACCTCTCTCTAATTTCAAACCTTTTTTATTCCACTC
CTCCTCTTGCTTATCCCTGGCAACCATTCTGCTTTTTGTCTCTATGGATTTGCCTT
TTCTGTATATTTTATATAAAACAAATCATGCAATATGTGACCTTTTTTGTCTGGCTTCTT
TCACTTATGTAATGTTTTTATGTTTATCCAGGTAGTAGCATGTATCAGTACTTCATTCC
TTTGCATGACTGAATAATGTTACCATACTTTGTTTATCCACTTATCAGTGGTGAACATTT
GAATGTCTTCTACCTTTTGAATATTATGAATAATGTGCTGTAATATTCATGCACAAAT
TTCTCCACGGATATGTTTTTCTCTTGGGTATAAACTGAGGAGTAGAATTCTTGGGT
CTTAGGTAATTCTCTAATCTTTCAAAGAACCACCAACTGTCTTTCACACCAACTGCAC
CATTCCCACTAGCAGTGTGGGGGGTCTGATTCTCCACATCTTTACCAACACCATTATG
TTTCTCAATTGTGGGCTAGTCTCACATTTGGAAAGCTAGTGGGAGCAGCGATCCATCTAT
TAAAAGTTGTATGAAATTGAGTAATGAGCCACCTCTCTCTTGTAGGGCTTATTATGTTCT
TGCTTAAGGCAATCTTCATGCATTGTGAACAGAATTATACATAAATGCTCAGATAAAAGG
GCAAACCATCTTAAAGGGAGTAGACAACCTAGAGGCAGGAGACCATACTGAGGCAGGAAG
CTGGGGTTTTTATGGTCTGTACTTTTGACTATATCTCACCATTGCTTTTGTCAAAGTG
AGACTAGGTCTAAGTTTTTTTTCAGGTATAAGGTGAGTGTGGTAATTAAGGGGCATGCTAG
CAGATCATTTTGGGTAATGCTTCACAGTCCACCACTGGTGTGTCAATTGTGGTGCAGATC
CAGTATCTTAGCTGTGTAATTTTCAGACATCAGCAATATTAGTTTAAACAAAGGCAATTAG
ATTCCAAGACAAAGGAATCGTGTATTATTCTAGCCTTATTCAAACCTTGATTATATAAATCA
GTTTAGTAATTTATTTATTTGTTTCTGTATTTATTTTATTTCTTTGAGATGGAGTCTCA
CTCTATTGGCCAGGCTGGAGTGTAGTGATGCAATCTTGGCTTACTGCAACCTCTGCCTCC
TGGGTTCAAAGCTATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCTAATTTT
TGTATTTTGTAGTAGAGATGGGGTTTACCATTGTTGGCCAGGCTGGTCTTGAACCTCTGAC
CTCGAGTGATCTGCCCCCTTGGCCTCCCAAAGTTCTGGGATTACAGACGTGAGCTACCG
TGCCCACTCAGTTTAGTAATGTATAACTGGGTTTTACCAGTTGTAAATTACTCTTTTG
TCGTGTTTTTTTGAAGACTGGCAATGACGGAGAACTAAAAGTGCCAGGCTGTTGCCTTG
TTCTGTATTTTGCCTTAGTTTTTTTTTTTTTTTTTTTTTTTTCTCTGAGACTGAGTCTTG
TTGTGTTACCAGCTAGAGTGGAGTGGCATGATCTCGGCTCACTGCAACCTCTGCCTCCT
GGGTTCAAAGTGATTCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGCCTGCCACC
GCACCCGGTGAATTTTTGTATTTTTTAGTAGAGACGGGATTTTACCATTGTTGGCCAGGCTG
GCCTCGACCTCCTGACCTCATGATCCACCAGCTTCGGCCTCCCAAAGTGCTGGGATTACA
GGCGAGAACCACCGTGCCCGTCTTGCTTAGTTATTTCTTGTTCCTCCTCTAGTCCTA
TAGTTCTCTGACTGTATTGAGGAAATGTAATTAATATTATTATGTTAATAGATATTTAT

FIGURE 14.10

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GTGGTTGAATATTAGAAATTCCTTATTTTGGTCACATATCCTGATCAGTAGTTGGTCTTC
TGGAGATAGTGATTTTTCTACTAGAGATGACTTTAGGACCTATTCAGGTTTTTTTAAAGAT
CCCAATTTAAGGAAAGACTATTCTCATTATTGATTTTGCTATATGCAGGGAAATTTATTT
CGAAAGGTTTTTTCAGTTGGCTTTTAGGGAAGATTATATATTCTCTTTTTTTTTTTTGGC
CTTTTCCACATGTTCTAAAAATGATATATTCTTTAACTCCTATGAAAATACATTGTTTC
AGTAATTGAAGATGCTGATTAAAGTCATATCTCTACACATTTTTTAAATTTGAGATAGA
TGGGACTTTGTCCCTTCTTACACCATTCACTTATTCACTTGGAAAACTATTATCCAATA
CTTATGTGGCAGACACTGTTTCTGGCACAAGGGATTTCAGCAGTGAACAAAACCTGCCTTTT
TGGAGTTTACATTCTACTAGTGGAAAGCGACAACAAGCAGATAGACACATTTCAGTATATA
ATTCAGTGTGATGGTGGTGGTAAAGTCCTATGTAGGAAGAAAAGCAGGGTAAGGAGGCT
TGGAGTAACTGGAGTGAGTCATAGATGGACTTGTGAGGAAAGGTTTCTGAAGAGGTGGT
ATTTGGGCAGAGATCTAAATAAAATGAAGCAACAAGCCATGAGAATATCCGGGGGAAAAT
GTTCTGGGCAGAAGCATCAAGCATAGAACTTGTGGTATGATATTTATTCTAGCACACATT
AATTTTAAAAATGTATAAAAGACATCCATTTAATCATATTAAAGATTTCATGATTTCATT
TAGACTTAGTCAGAAACCAAATTTATATTTTCTTTTTAAATAATTTTATCTCAACTCTTA
TTTTACCCAAATAGGGGCCAGAGTTACTCAGCAAATACATTGGAGCAAGTGAACAAGCTGT
TCCGGGATATTTTTATTAGTTGGTTCAGCTATGAATGTTTTTAAAGTAACTGACTCTGTTA
TTATTTATCAATCAGTGCCTTTTTTGGTCTTGTTTTTGAAGAACTGATATTTGAAACCT
GTGGTTTTATGTGAATTATTAATAAGCTAGAGGACGTGGATTCTCTATTTTCATCAAATAAT
ACAAAACATTTTAGATATTTAAATTTTGGAAATTATTTGGTTTTGTTTTACAATAGAAATA
CTCCTCAAAGTGAATCGAAGTGGTTATTCAAAGAAATCTCAGAGTAGATTCTTATATGA
AGCAAATAATTGCCCTAATTTATCTCTAAATTTTGTAAAGTTCTAAATTCCTTTTTCCCC
CAGTTTCTAATTTATCTCTTATAAGTCAAGAGTCCATCTGGCCAAATTTAATTTCAGTGAG
TGTAAGTATTTTGCATATATTAATAAACTGTATATGAATACAGAAGATGGTATTTAAGGA
TGAAAATAATTATTCAAATGTGATAGCATTATGGGGAGTTTTTAAATAAAAGTTACTGTT
TTATTCCTTCCAAAATTTTATTATAAAGTATACAGTTAAGAGAATATACATAAAATACAT
ATGCAGCTTAAGGAAGAATAATAAAATGAATACTTCATGTATTCACCACCGAGTTTACCA
GGAAAAAGCATAAAACAAAATAAACCTCTTCCACGTAATTCCTGGGTAAAGAGAAGTTAT
AGTGGAAAATATTTGGGAGCAAACGATAATGAAAATACTATCCATTAAAATTTGTTAGATG
TTGCAAACTGATTTCAAGGAAAATTTATAGTGTTAAATGTTTAGAAAAGAAAAAGGTT
AGAAGTTAACCCTTATGTATCTATCTCATGAAATTAGGAAAATTATAGATATAAACTAA
AAAATATGTTAAAAGGGAATAATAAAGATAAGAATGAAGTTTAAATGAAACACAAAACAG
AGAAGCTCACAAAGCCAAGATTTATTTTTGAACACCGAGTACAATTGACAAATCTCTAA
CAAGTTTGATTAAGAAAAAAGAACATGAATAAACAATTTAGGGATAAAAAGGGAAC
ATCGCTAAAGATATCCCAGAAATGTAAAAGATAATAAGGGAATATTATGAAAATATTCAT
GCCAATACATTTGAAAACCTTAGGTGACATAGACAAAAACAAAATTGACCAAAATTGAGCA
AAAAAGAAAACAAAATCTGAGTAGTCTGTAACTTAGTAAAAATTGAGTTAGAAAAGTTAA
AGAAGTCTTTACACAAATCAAACATCAGACTCAGTTTTCTAGGAGAGTTTTGCCAAACAT
TCAAGTAGCAGATAATTCTGGTCTATTTTTGGCCCCAGAAGATATATTTACTTGCCATG
CATTTAATGAGATAGCTGTTGATTTTTTTCAATCACCGTGACAGGTGTTTTATATTAGGT
GTTATTCGCCAGACATCTAGTCCACCTGTTGCCAGATATGGAATTAATATTCACTTATTT
TGAATTTAAATTTGTTAATAAATTAATAAAACAAAGTCAAAGTTCAAATTATTAAAAAG
TAAAAGAAATAAAATATATTTTATAGAGAGCCCTTACAAAACAGTACCAACATAATGAGC
TTTCCAAATTTTGAATGGGCAAAATAAATGAATAGGCATTTACAAAAGAAGGAAGGGTG
GCCAATAAGTATATATTAATATAAAAATGGTTACTTGTAATAGGAATCAAAGTGTGTTGA
CTTATTGACTAAGAGTCAGTTTTTTGTTTTGATCCCTGTAGTCTATCCAGAAGGCATGGG
TCTTAATAAAACACCTTGACCTCAACAGTTTACTGAATACAAGGGTAATTTTCATATGCCTT
GCCTTCTTTAAGGGTTTTGTTGTAAAGATTAAAAATAAATACATAAATATATATAAATACAT
TTATATGTATTTATATGTAATTACATACAACCTTGCCCTCTTTAAGGGTTTGTGTAAAAA
TTAAAAGAAGTATATAAATATATATAAATACATAAATAAATACATTTCATATATGTATAT
GAAATCACTTTGCCAACTATGAAGCCTGATTCAAATATGAAATGTTGTTGTTTTTCCCA
GAGCACAGGCTGCAAAGCCCTGCATTCTTTCTTTGATGAATTTGAATCCATTGCTCCTC

FIGURE 14.11

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GGCGGGGTCATGATAATACAGGAGTTACAGACCGAGTAGTTAACCAGTTGCTGACTCAGT
TGGATGGAGTAGAAGGCTTACAGGTAATAATTATAAATACAGAAATAGAATGTTATAAC
AAAATGTCATCATGTGTCATCAGATTTTGGTAAAAAATGTTCTTTTCTCTAGGTGTTT
ATGTATTGGCTGCTACTAGTCGCCCTGACTTGATTGACCCTGCCCTGCTTAGGCCTGGTC
GACTAGATAAATGTGTATACTGTCCTCCTCCTGATCAGGTGACAATTCATATTTAGAGT
CCAAAACCCAACAAATGTACACTCTTTCTTGTGAGCTTTACTTCTGCCAGGTAATGGC
AATTGTCCTTAGAAGACCAGCTTTCTTAGGGAAAAGCTTTAGCCACTGTTTGTCAAAGC
ATAAAAAGATTCTGAATTAGATGCAAAGCCTTTTTTTGGCCCAGTGCAAGTCTGAAAAC
TTGTAATCCTTCTGTGTTGGCTGATTGGGGAAAAAATGCAAGAAACCTAATGTATTA
TATTTTCACATTATCTTCTGTTCAAAGATTACATACTTCCATTATCCTGTCAAAAAA
ACTCTGATACAGAATCAAGCATGTGAATCGTAAGCATGTAAGCAGGTTTCATAGAGATAA
TTTTTCAACTCTTCTTGTCTGTGTTGTTCCAACTCTTATTCTCCAATTTAGAAGCAAA
CAAATAAATGAATGAAAGAACAGATAGACAAATGAATAGTCAAAGGTATAAAGTATCTGT
ATATATGTTACATGTAGCTATTATTTAAATTATTTAGATTTTCTTTTGAAATACCTTCT
TGGCACACTTGCCTAAATCTAGAAAATAAGCACTGTGTGAATAAGAAATTATTTACACTG
AATATTTTGTAGGTTTTTGGGTTTTTGTGTTTTTTCAGACAAGGTCTCACTTTGTCACCCAGG
CTGGGACACTGGTACGATCACAACCTCACTGCAGCCTCTATGGCCCAGGCTCAAGCAAT
CTCCCCACCTCAGCCTCCCGAGTAGCTGGGACCACAGGCACACGCTACCATGCCAGATA
ATTTTATTATTAATTTTGTATAGAGATGGGGTCTCCCTGTGTGCCCAGGCTTTCTTGA
ACTCCAGGGCTCAAGTGATCCTCCACCTCAACCTCCCAAAGTGTGTTGGGATTACAGGCGT
GAGCCACCATGCCCAGCCTTAAGAGTGTGTTGATTTTCATTCATTTTCTATATATATTAT
TTCTGTGGGGAAAAAATCCAAGGAAGATAAATAGTAGGCTGTTGGTACATTTCTCAAC
TTACTTATAAAGCTTTTGTATATATAAGGTTAATTTATGAAGAAAATCATAAGATACAC
AATTTAAGATAATATTTTAAATTTTATTTTATTTGTTAAATAAATTTTCTCCTTTCA
GGTGTACGCTCTGAAATTTTAAATGTCCTCAGTGACTCTCTACCTCTGGCAGATGATGT
TGACCTTCAGCATGTAGCATCAGTAAGTACTGACTCCTTTACTGGAGCTGATCTGAAAGCTTT
ACTTTACAATGCCCAATTGGAGGCCTTACATGGAATGCTGCTCTCGAGTGGACTCCAGGC
AAGTTATATGAGGAAGTTGTTATGACATTTTATGAGTGATAAAGAAAGTACAATGTCAAA
ATTTCCACCTTAAAAAATGCTATTTTTTAAACAACCTTGGTAAAACTGTATAGAAACATA
AATTTACCTTTAGTTGAATGTTCCATAGTTGGAATATGGGTTTTGCAGAGAATTTATAAT
TATGAAGTTTGATGTCTGTTTCTTTAACATTACCTTAATATTGGCAAAAAACATGTTGGTG
TTTGCAAGGATATTATTTAAATTGGGATACCATGAATTAATACTACAAACAAAAATAAT
TAGAGTTTTTGTGTTGTTGTACTTTAACTTTTAAAAATAATCAGTTAAAGTTGTTGTT
TTGAAGCTCACATTGTTCCAATCTGGCCAATAGGAGCCCCCTTTGTATGGCTCCTGTATC
TTTATGACATGTCTCATCATTCTGAATCACTTCCTCACTTCAGATACAGTAAGTTAT
TCTTGGCCAGGTGCAGTGGTTACGCCTGTAATCCAGCACTTTGGCAGGCCAAGGCAGG
AGGATCATTTTGGGCTAGTTTGGAGACCAATCATGGTTGCACAACTGTACCCACTATGG
ACAACAGAGTGGGATCTTGTCTCTGTGAAAAATTTAAAAATTAGCTGGGCATGGTGGCAC
ATACCTGTAGTCCTAGCTTCTTGGGAGAGGCTGTGGCAGGAGGATCGCTTGAGTAAATCC
AGGATGCAGTGAGCCATGCTTGTGCCACTGCACTCCAGCATGGATGACAGAATGAGACCC
TGCCCCCAAAAAAGAAAAATATTCTTGGTTTATCTTGTACTTTCTGTATCCCAGCCCTAG
CATCAGCCTTTTCTCTAAAGACAGTATTATGATTTTAAATTTTACAGTAGATATTGAAAC
TGTTACATTATAGACTTTACCATATATTTTCTAGGAAGGATTATTCTATTACTCTTCTTT
ACCACATTTGTTTGAATGTCTACAGAACCTACAGTTTCTAAATCAGAACTCCCTAGGT
TTTTGCTATTTTGGCAAGCCATTGAAGTTCTTCCCTCTCCCTTTACTACCAGAAAGGTGT
GTATTTGTAGAGCTCTCTATAATGAGAAAGCACTCTATAACATGGTTGATTCAATTTTT
GGAGTAGAAAAGTATGAATGGAAAGTCAGAGACATAAAAAATAAAGCCCCAGAGGTCTGAGT
CTTAGCTTCATTACAGACTTTCTTGGGGGATGGTTGGTAAATTATCTACACATTCTATCT
TGTCTTTATAATTTTAAATAGTTAAATTTTACCATGTGCCTCAAACCGTTAGAGAATTA
ATGAGCTCTTTGAAAAATGCTTCTAAGTTTCTTGTATTGCTCTAATAGAATGCTATCTAT
GTTATTATTTATTTCTGAGACTAAAAATGTTTACATCTTTAACTGGTTGTCCTTTGTG
TATTTTAGGATGGAAGTTCCAGCTCTGATAGTGACCTAAGTCTGTCTTCAATGGTCTTTC
TTAACCATAGCAGTGGCTCTGACGATTACAGCTGGAGATGGAGAATGTGGCTTAGATCAGT
CCCTTGTTTTCTTTAGAGATGTCCGAGATCCTTCCAGATGAATCAAAATTCAATATGTACC

FIGURE 14.12

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GGCTCTACTTTGGAAGCTCTTATGAATCAGAACTTGGAAATGGAACCTCTTCTGATTG
TATCTTGTGCAGTCATCATTATACAGTTCTGAAATATAAAGCTATATGTTGGTGTAAGT
TGCAGTGATTTCTCTCCTAACCCAGCCCCACATATTCTCCTGGTTGGTTGGTTCTTCAGT
AAAATAGTCTTGTTTCTTGCTTACACTAATTGGTAATTTGCATTCTTGTTAAGATTTTC
AAGACAGGGCTGGGAGCAAGGAACCAAGTAGCGCGTGGTTGTGATTACCTTTGGTTTCT
TTGAGGTTTTCTCTTACCTAGTGGCTTTAAACATCTTTAGGAGCAGTTCCATTTTATAGT
AAACTTAAATTCTGTTATCATGAACAGTTGAGGATAATGAATAATTTGATACAATAATGT
AAGAAATTCCTGAAAACAAAGTGTTATCTGTGATACTTTTGCTGCATAGTAAGCACAATG
AAGTGTACTGATAATGTTTCAACAGGAAAGTGTTTTGATTAAATGTGGGCAGTATCACTG
TTCTACTAGCATTCACATCTCTTCTAAAAATTAATAGTGGTTCACTGTAATTTTATTGG
TACATGTAACATCTGTACATGTGTTTGGTTATCTATATGTTTCTGGTTTTTTTGTACATT
TGCTTTATTAATTTAGGCTTTTTTTTTTTTTTTTTTTTTTGGAGACAGTCTCACTCTATCATC
CAGACTAGAGTGCAGTGGCACAATTATGGCTCACTGCAGCCTTGACCTCCTGGGCTTAGG
TGATTCTTCCACCTCAGCCTCCTGAGTAGCTGGGACTACAGGCACATGCCACCATGCCCA
GCTAATTTTTGTATGTTTGTAGAGACGAGGTTTACCATATTGCCAGGCTGGTCTCAA
ACTCCTGGGCTCAAGCTATCTGCGTGCCTTGACCTCCCAAAGTGCTAGGATTACAGGTGT
GAGCCACTATGCCTAGCCTAAGCTCAGACTTTAAAAATATAAAGCAATTCATTTTTATTTC
CCAAGAACAGTAAGGTGGTGGTTAATTTTAGTCTTTAATCTGTTTTTAATTTATTCTA
TTTAGAAATGTCCAGAACTTAGTATACTTTACTTTCTGAAAAATGAAGAAACCTGTCC
TTGGGCATTAGTGTGTTGGATTAAAGCAACAAAGTTAAAAAAACCTACCCTGTGTTATGG
CAATTTTCACTTGATGGTGGTTCTATAACACAGGTATCAGTGAACCTTTATAAAAGATGA
ACAACCTTTTCAGCTTGCTTAATTTCAAGTAAATTAACATGTATACTTATCTATGTTAATGT
TTTTATTGCTTAAATGTTAATTTTATATTTGGTAAACAGATAGTTTTTCTCTCCCCC
TCTTCTTCCATCTTTTCACTACTACAATTTACCATGCAGAGCTCACAATGTCTCTCTGCA
CCAAGCTCCATGACTCAGGATTTGCCTGGAGTTCTCTGGGAAAGACCAGTTGTTTTACAG
CCTCCAGTGTTAAGGACAGCTTCACAAGAGGGTTGCCAAGAACTTACACAAGAACAAGA
GATCAACTGAGGGCAGATATCAGTATTATCAAAGGCAGATACCGGAGCCAAAGTGGAGTA
TGGCTTTTTCCCCCTCATTATAATTGTTAAACTTCTTAAAAATGTTTTACCCCTTTTGA
TATATATTTCTTTGACTTATAAACGAGCTATATTTATAACAAGGGACCAGAACACATTA
ACTCAGTCATGGTTATGTGCTTCTCTTCAATGTTTCATTATCTTATAAGGAAGAGA
ACGTATGGTCTCTTGAAAAACTGACAATAAGAAGTAACAACCTGGACTACCACATTTTTT
TTTACATCCTTAATTTAACTCTTCGTCAATTTCTTTTTTACTTAAGGAGGACGAATCCA
TGAACCAACCAGGACCAATCAAAACCAGACTGGCTATTAGTCAGTCACATTTAATGACTG
CACCTGGTCACACAGACCATCCATTAGTGAAGATGACTGGAAGAATTTGCTGAGCTGT
AAGTAACAGATTCTGTTTTGGAAGTACAGCTACTATTACAAGTGACATAGTATTACACTT
AAACCTTTAAAGTTCTGTTTTAAAAATAAAAAATATTTTGAATATTTAAAGCTAATTCAAA
AAATATGTGTCGTAGCTATGCATTAAAAAACCCCAAAATGTGAGAAGTACAGAAGTCAAA
ATTGAGTTTTTCAATTAACAGTTCATTTGATTATATTTGAATTATTCATAATGGACTCATT
TAATTTTAGTAACCTTTGGGCTGGGTGCTGTGGCTCATGCCTGTAATCCCAGCTCTTTGGG
AGGCCAAGGCAGGTGGATCACCTGAGGTGAGGAGTTCGAGGCAAGCCTAACCAACACGGG
GAAACCCCATCTCTACTAAAAATACAAAAATTAGCCAGGTGTGGTGGCATGTGCCTGTAG
TCCCAGCTACTTTGGGAGGCTGAGACAGGAGAATTGCTTGAACCCAGGAGGTGGAGGTGTC
AGTGAGCCGAGATTGCACCACTGCCTCCATCCAGCCTGGGCCACAGAGCGAGACTGTGT
CTCAAAAAAAAAAAAAAAAAAATTTAGTAACCTCGAAGAAATAAGAAGGAAAAATTTAAAGT
TGAAAGTGATTCTAATGTATAGTTTATAAAATTTTGTATAAAAATACCTGTTTTGCCTT
CAAAATAATTTATATTAATATTTTATTGACCTCAAGAACATTTAAATACATTCAGATTTA
TTCATTTGTGGACCACATTTGTTATACATTGGATTTAAAGGATCCTTGCAATTGAGTTTA
TGGCCACCTATGCATCTGAGACCCATGGACTGGGAACCATTTAGGTCAATGATTCAGTG
TGATTCAATTTAAGAGATGTTTATTCCTGGTCTTTAGAAGCTGCTACCTTTTGTTATCTA
ATTTTGCAGTACTTTGAAGTATGTATGTATGTGTACATACGTTAGTGCTATGTATTTATT
AAAGAAGAATCAGAAAACAGAGGTAAGGAAAAATAAGGAAACAAATTTCTGTTAAGCCCA
CCACCTCCCAAAGCATATTTGTTTATATGCTTATATATGTTTTCTTATTATGGTAAGAAC
AGCTGTACATATTGCTATATAGCAGTCCCCCTTTATCCACATACATCCTGAAAATTGTT
TTACATTTTAAATGTTAACTACTTTATTGTTTTTAAATGTCATTTTATAGTGTAGCTATG

FIGURE 14.13

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CCACAATATCCAATTTTTAGACATTAAATTGCTCCCAGGCAATGTGGTAATGAACATTCTTGCAGCTGAATATATGCACATATCTAATTGTTTCACTAGGATAGAGGTGGAATTGTATAACAGGGAGCTCACATTTTTTAAGGCTTTTGAAATGTATTGCCAAATTGCCTGCCAGATATACTGCACCATCACTAACATTGTGTGTTGCAGTATTTTTCTAACTTGGCCCTTTTGATTTAGAAAAATGATATCAATAATTTACATTTCTTTGATTAAAGTGTAGAAGTTATAATTTTTCATATTATTCATTGTCATTTGTATTTATCTTTCTAACTTGTCTCTTCATCCCCTTTGCTCCGTTTTCTATTGGAGTGAACCTTATTTGTAAGAATTCTTTTAATTTCTGTGACTGGAATTTTTTTTTCTAGTTTGTATTTCCTGTTTCAATTTCTTAAATATAATTGTGTTTGCCAACAATCCATTATCTTTGTTTTGTAATGGTAGTATTTATACATATTAAATTATCTCTTTCTTTTTTCAGATATGAAAGCTTTCAAATCCAAAGAGGAGAAAAATCAAAGTGGACAATGTTTCGACCTGGACAGAAAGTAACTTTAGCATAAAAATATACTTCTTTTGATTTGGTTCTGTTAAGTTTTTTGATGGCTTTTCCATATGTTGTAACAGGAAAAAATGGTGTCTATGAATTTCTTCTTAATTTAACAAATTTGGTTAATTTATAAAATCACAGATTGGTAAATGCTATAATTATGTAATGATCAGGATTGAGATTAATACTGTAGTATAAATTTGGGACATTATAACAGATTCCATATTTTATTTCTTAAATCTAAATTCAGTCTTTAATGAAATAATATTAGCCAAATGTGGAACATAATTTATTTCTTTGAGGAAAAGATAATAAGAATGTAATTAAATTTAAATTTCTTGGAAATCCCAGTTGTATATTCATCACCTTTGTAGCATTTGACAAATTTATGCTTAGCAGCTTCTTCACTGTTTTGAAATAAAATATCCTATTACCTACTGATACAATTATCTGTTCTTTGTATATCAAAAAATGTGAAATTTACACATAATTCAAATACATTAAATTATCCGCTCAACCAGAAATGAAATCACATCCCTCTACTATACTACATCCAGCTCCAAGCCCAAGATATTAAATGACATCCATTCTCTCTAGTTCCAGTTATGATTTTATCTTGATATTCTCTCATAATGAACATAAATTATAAAGTTAGCCACCATCAATACAATCTGCGTATCTAATATCTTAACATATAGTAATGGGGTAAGGGAACAGCAAAAAGGAGAACATTAATTAATAATACAAAGTAGCCTGGGCAACATAGTGAGACCCCATCTCTTAAAAAATAATTAGCCATGCATGATGGTATGCCTCTAGTCCCAGCTACTTGGGAGGCTGAGGTAGGAGGATCACTTGCTCCCAGGAGGTTCAGGTTCTAAACCAGCAAAGCTCAGAATCCCAGGGGATAGAAACAAAGACTTAGTGGATCACTAGTATTAACTGAGACACGTCACCCTGCATTGCATTTGTTTCTCAGTTCTTTGATGAAATCACTGAGCTGACATACCTGCCCTCTTTTACCATAAAGTGAGTTTCATGATCAAGCAATGTCTATGGGATAGCCTAACAAACAATGTAAAAACCATTAGTAAGTTTCATGAAGGGTGGTGGTGGTAAAAATTTGGGAGAACATACAAAACAAATACAATTTCCAAGGTGTGTCCTCTCCAGGAAGGACAAATTGCTGCCTGCTCTGTGATAGAAGAGGATCAGATGTAATCAACCTGCCGTGAGACTTGGGCTGTTCTCTCTGGGTGTGGACTTGCCTGGTTGGTCACTGCTGCTGACAAGTAGGCTGTCAATATAGCTGGGTTGTCTCATGTGAGCTGTGGTGAGGGGAAGTCCACATTGTGGAGGCCACATCCCTGCACTCTTGGCCAATTTGACCATGAATCTTAAGCACGGGGTGGCTGGAAAAGACAGCCGATTGACATCCATACAGAGGTCACTTGACCACTTGATTAGTAAAGCACTGGAAGGCTTTAACTGAGCATTACATAGGACACAAATATTCTGATTCTTTGGGCCCCATTCCAAGAACTCTGGGCATACTTTTCTCCAGACCTCATACCCAGTTGTGTTCTTTCCAAATTTCTGGTCACTCTGGTTATGTTATTAGCCACTATCTGTAATCAGCATAGATTTTTATATCAGACATCTCTACCTCCTGACAGAATGGAGGAGATATGTTACTTAACAATTCTGTTCCCTTGGAAGATTTCCCTGTCTCCACTGTTTGTAAGGGCTACTCCCTCAATGTAGCAGTAATGCTTTCACTCTGATGGGAAGTCACAGTGGAATTCTGGGTCTCCAAGAATTAGTGTAGTGACATACACAGTGTCTGATAATCCCCAGAGTGTCTGGTGGCCTTGATCCTGTGAAGAAGGCTTGAGAAAAGAAGATTGATGGCAAGAAGTGTGATGTGATGACAGGGCCTTTCTCTGGCTCTTCATTCTTAGTCTGACCTAGGTGTGAGAATTAGGTCAGGGGCCATGACTATATTGTGGTGACTCAAACCAGGCCCTTTGTTTACTAACTGGGAGATTTTACATTGTAAGAATCAAGTAGGATCTTTGCCCATGTATTTGGTCTTAAGAACACAAATGATATGGCTCCAATGACTGGAGGAACACCAGGGTCTTGGTCTCACGCTGATTTAGATAAAACGACTGTGAGGCCTCTGAGCCCAAGCTAAGCCATCCTCCCCCTGTGACCTGCACGTATACATCCAGATGGCCTGAAGTAACCAAGAATCACAAAAGCAGTGAAAATGGCCTGTTCTGCTGCTTAAGTATGACATTCCACCATTGTGATTTGTTCTGCCCCATCTTAACTGAGCGATTAACTTTGTGAATTCCTTCTCTGGCTCAAAACCTCCCCACTGAGCACCTTGTGACCCCGCCCCCTGCCCTAAGAGAAAACCCCCCTTGATTATAATTTCCACTACCCACCCAAATCCTATAAAATGGCCCCACCCCTATCTCCCTTCGCTGACTCCTTTTTCGGACTCAGCCCGCTGCACCCAGGTGAATAAAGCAGCCTTGTTGCTCACACAAAGCCTGTTTGGTGGACTCTCTTCACACGGAC

FIGURE 14.14

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AAGCTTTAGTAGAGATCTCAAAAATGGTTGGATGGTAGCAAATTACTAAGAACTCTCAAA
GTTTCTAAAGCCTTAGTTTTCAGCTTGCTAGAAAACCTATGTTGAGTATTATGGCTAGTTC
CATAGTTGAGTTGGGAAATGTCTTTGAGGAGACACTTTTTCACTTTGTATTCATCTGTAC
ATTTTCTGTTACTTGCATTCTGTCTAGCTCAGGCTATTAGAGCAGGTACATTTTATAAC
TGGAATGTTTATGTGTAGTGAAGCTCTGAGAGGACTTTGCATTAGATCTCAGCAGCATAA
TCAGAAGGTTGTCCTTTGTCTCAGCAATTTTAAAGCTAATAGTAGCAGAAATTGCAGTGG
AAATAGACTGCTTTGCCACAACATTCAGAAAATCATTTATCTTTTTATGTCAGTTCTTGT
CACCAAACAATACATTTTAGTACTTCTCAAATTGCAGAACTCTCATAGGGCTGGGAAAAT
GCCTGTAGACACATACATACTATGAATGTGCTAATGTTTTTGTATTTTCATAGCCCATC
AAAGCTCCTGAGTCAGTTTCCACTATAATCACTGCAGAATCAATCTTCTACAAGGTAAGC
TTTTGTAGAGTTACTGAAGGAAGAGTTGGGCCTAGTGGGTAATGTGCCACTAAAATGTTG
GATTAGTCTAAAGGTCTCTGCTACTCTTTATTTGTATAAGGTGTGATTATACTTTTTGTT
CCCTTCTTAGCTGTTTTCCCCCATAAGTGGCTGTTATTTAAACATCTCATCTAGAGCTGA
AGTGGGAGGAGAAAGTGCCTACTGACACATGATGTGAGGATCTTAAGTATTTTTTTTAG
TGATGATTAGGAATTATTCTTAAATGCTGATTGTATAGTGTGGAGCCATGGAAGACT
GAGCCGTTAGTGCATGGCATTGAAGAATGAGAAGGACAGAGACAGGATTTGGACTAGTA
GAGGTTGTGCACTGTGGTGTCAAATGGGTAGAGTAGGCCAGAGATTCTAAAATGCCTTT
AAGTGGAGTTGAGCTGAGTAAGGGCAGTAGTGAGGATTAACACCTACTAGAAAATTCATAG
TGAGAGGAATTCCAAGATGTTTTGATAAAAAGAAATGAGGAGGTGAGGTTTCCAGGGCCAA
AGTCCATGAACATCTGATACCTCAGTGAGAGAAGTGACAGATTGTTGTGTTTAAACCAGA
AGTCTTAGGAAAGGAATTAGAACATAGACCCCCAAGGCTCGGCAGGCCTGGCACGGCACA
GGCAGCAACCATTGAAGGCTATTTGGTGTTCGGGATCTGAAGTGTCAATTAGGGGACAG
TGGTGTGAGTTAGTACTTTATACTTGACCCAGGTGGACTGAGAACTCAAGTGATGATGC
CCTTAAGTATACTTTTTTTTAAAGCCACAATCTATATAGTCGAAGTCTGTTCTCTCCCAAC
AGGGGTACACTGGCATTCTCTCAGCAGGGCTGGGAAAAACCAACAACAAAAAAGTCTGTA
CACAGGCAAACATCTCTCTTATTTTTCCAACATTTAATACATTGTTAATAAAAATATCTAA
AGTTTAGCAAACAGTTGCTGTGTATCAGTGGCTGAGCATTTTGCATGCTTTATTTTCATTC
AGTTCACTCTATGAGGTGGATACTACTATCCCCATTTTCTAGATGAGAACATTGAGGCAC
AGCGAGGTTAATTAACCTGTGCCAAGATCACATAGCCAACAAGTCATGGAGTGAGGCAGTC
TCATGCCAGAGCTTAAGCCTAGAGCATAGTTCTCTGGCTCTACAGCTTTAGCAAGTGACTG
GCTATGTGACGAGGACCAACCTCTCTAATGTCTCATCTGTAAAATAGGAATTGTAAATAG
TTACTACCTCAGTGGGTCAAATGAAATCATATGTGTTAAGCACTTAGCAGAGTAAGCACT
CAATGAATAGTAGGAGTTATCATCTCTCGTATTTGTGCATTACCTTCACAGTTTACAGA
TAAAGCCAGAGAAGCAACTTGTGTAGCTACGGGTTTAGTGTACTAACAGTTTCCATGTGTG
TCTCCATGGAAGGGTGTGTGGGACCTGTTATTGTGACTGTCTGTACTTTCTGATTGTTGT
CTGCCACCCATGTTTTATTAAATGATAAGGACAATAATGCAACAAAGTAGTCAAGTAATGT
TGCAAATGCCAGTATTGTAGTGGCTATCACAGCAGTGCCACTGGCAGGCAGCACCATGG
TGGCAAGTTCAAGAGGTCACTGCCAGCCACTGAGCTAGAGCCAGATCAGGCATGCAAGA
GGAGCCTGAGTGGGAGCCACTGGGGATCACGGCCAAGAGTGTGACCACCCAAGACCCAGA
ATGGCTGAGTGGCCTCCCTGGAGCATGGCAGTGGCAGAACAACTCCATGAAGTCAGATCT
GGTGATGCCTAACTAGTGCTGTTCTCGTGTGGACCCCTTTTCTCTACCAGAAACCTTGA
ATCCTCTCAGCAAATGAGGAGACTACTCAGATCAGTGACTTAGTCCTGTTTGGTGTATA
TATGTGTACACAACACAGCACATATTAATAAATACCTACTATGTGCCAGGCACTGCCTAC
CACTGGAATCTTTCACTAAGACATTTGTTTTACTTTGCATTTCTGCCTTTACACTATGAA
AGTAGATGTTTTGGATTATATTCAATTCAGCATACATTTGAATATGCTGTGTTATGCATA
GTAAGCCTATGATAAGCAAGTATTCTCATTTAGAATTTGGGAATATTGATTATACATGTG
GACAAACAAACCATAAATGCAAATTTTATATGATAAATAAATTTGGACTGATGGCTGG
GAGGAAGGACCAGCTATTGATGGGTAGGAAGTAGCAAGTAGCGGACTGTGGCCTGCATAG
ACCAGACCCATCCGTAGTGATCCAGATGAAACAGCCACCCTCAGACACTTGATAAAGGG
TCCACCAGGAAAAAATCCTGGCCTATCAGGTGCTATGTTACAGTTTCAGTTACTGGAAGT
ATTTCTCTCAAAGTGTTTTTTATGGTTGAGGTACACATTCTACAGCTTTACCTGCTGCCA

FIGURE 15.1

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AGTCCCTGTTTCAAGGGAAGCAGCAATGAATTACACTGTTCCCGTAGTCAAGGACAGTAT
ATCTTACCAAGAACTATAACCCACTTAAGGAGGTGCTGGATGTCATAAAGATTGGATCAA
CCATTATGGGTGTTTCAAGGAGAGATTATTTCCAGCTCAAGACCCAGGGAAGAGGACATA
GGATGGATAACCAGAGTCATAGGGAGGATTTAACACAGGACATGTACACATTAGTTAGTTG
GGTATAAAGTGGAAACAGAAATGAATGAGACACAAAGCCTTGAATGCCAGAAATACTAGTA
GTCCTGTTGTGGAAGGATATAAACTCAACTGGGAGTGGAAAGAGAAAGGCAGCAGTGAGT
CTAGGAGATGTACAGTAGGTTGAGGTAAACATATCCTGAAGACTATAATCCAAAGATTAT
TTTTGGTTTGAATTTGTTTGGTTTGAATTCATGGTATCTATTTTCTTTGAGTGGATGGT
TGGGGAGGGTGGCATGTAGAATGCATTCTTACCAAATCAGCATGATTTTCAAGACAGTAC
AGAGAAAAGACTGCTGAGCTGATGTAGGAGCTTTGGCTGCAGTCTCTATGGCTTTCAGCA
AGCCGTTTAACTTACTACTGCTTCATGACTGTGGCTAACAAAGTAGGGATAGTACGGAG
CACAGAGGATTTTAGGGCGGTGAACTATTAATACTCTCTTTGTATGATACTATAATGG
TGGGTACATGTCATTATACATTGCCCCAACCCACAGAATACACAGCACCAAGAGTGAAC
CCTAATGTGAACCTCTGGTCTTTGATGATGCTATGTCAGTGTACGTTTATCCGTGTAACAA
GTGTAACTCTAGTGGTGGGAGGGGTTATTGATAATAGGGGAGGATGTGCATGTGTGGG
GGCAGGAAGTATAGGAAATCTCTCTACTTCTGCTCAATTTTGCTGTAAACCTAAACC
TCTGTAAAAAATAAAGTCTATTTTTTAAAAAGTGGGGATGGTATTACGGCAATATAAAAT
CAAAATACTTTATGAACAAATCTTTTCTCCAGATGTAACTGTCTATATATGCACCCTCGT
ATGTGTATGTATAATTTTCATTCAAACGTGAAACAACTTTAGAATTGGCACCAAAACATAT
AAACACTGATACATTAGACTATCTCGAACACCTTTTACTGACCCTTTGAAAACCTTGCTT
ACCTATTAAGGTTTATTTCATAGCTGTGATGTTCTATTTTTTATTTTCAATGTGGGATTATC
TTCTGTTTCCCCCAGGGAGTATATTACCAAATTGGTGATGTTGTTTCTGTGATTGATGAA
CAAGATGGAAAGCCCTACTATGCTCAAATCAGAGGTTTATCCAGGACCAGTATTGCGAG
AAGAGTGCAGCACTGACGTGGCTCATTCTACCTCTCTAGCCCCAGAGACCAATTTGAT
CCCCCTCCTATATCATAGTAAGTTTGACAAATGGCACAGGTTTTTTTTTAACCTAGTT
AACTCTCCAATATTATGTAAAAGAGTGTGTTAGTCAGCTTGGGCTGTCAGGACAAAATAT
CACAGACTGAGTGGCTTAAACAACAGAAAGTCACTTCTCACAGTTGTGGAGGCTGAAGT
CCAACATCAAGGTGCTGGCAACACGGATTTCTGGGGAGGCTTTTCTCCTGGCATATAGA
TGGTCACCTTCTTGCTGTGTCCTCACATGGCCTTTTATGGAGTGAGAGCTCTTTGGTGTA
TCTTCTTATAAGGACACCAATTTCTGTGAGATGAGGGCCCCACCCTTATGGTTTCATTTAA
CCTTAATTGCCTCCCTAAAGGTCTCATCTCCAAGTACCATCACATTGGGGATTAGGGCTT
CAACATATAAATTTGGAGGGTGGCGGGGGGGGATGCAATTCAGTCCATAACAAAAAAGC
ATGAGTATTATTAAAGTACAAAAAATTAGAGAGCTTTATAGAAAATATGAGGCATTTTAT
GTAGCTGGAGTGTGAGTGCTATCAGTTATTTTGGAGTGACCCAGGGTTAACTGTACTACAAGAATGTA
AGTGGTATGGATAAGATTTTTTTGGAGTGACCCAGGGTTAACTGTACTACAAGAATGTA
TTGCTCAGGAAGTAGGTTATTTAGGTTACTTATTTATACAAACCTATTCAAAAATAATTT
AGGAAAGAACTATCCCAGTTATCCCATACTTGCAAATCTCAATATGTGTGCCTCTGCAT
GCTACACATGTCATCTTAGGCCTTTATAGTATAAAGGCTGATAGTTGAAATGGCAGCTGC
TGTGCTTTTGTAAATTTCAAAGCTGCCAAAACAGTTGTGAGATAGACTCACAAGAATTTA
CTGATTAATACAATTTTTAAAGTTTTTCAAGTTTTTACAGTTACTTCAGACTTTTTATCTT
TCTGCAGTGAGCATGCATCATTACTTTTGCATCCTGAGAACAAAGCATAAGTGTGTTTTG
GAGAGAACTCCAGGGACAAATAATATACCACTGTTATTCTCACCTATATGTCAAGTTTGA
TACATTACCAACAATTTCTAGCCTTCTGCTTATAAGTATATAGAATTTTTATTTACCTTA
TCTATGGATCAGGATCTCAGCAGAGGCAGTGATGTATCAGAATCACCTTCGGGATTCTCT
TACTGCCTCCTCTTTCTAATCCCCAGATTCTGATATGCATCCTTGCTCTACAGCGAGGCA
GCATGGCATGAGGTGAGAACACCAAGTTCTGGAGCCAGACTGTCTAGGTTTACAGCCTGCC
ATTTACCGGCCATGTGACTTTGGCAAGTTTCTTAGTCTCTCTTGCCCTCACTTTCCTCATA
TGTAATGGGAATAATAAGTGCCTACCTCAGAAGGTTGATGTGAGGAATGAAGGTAT
TGATACATGTAACTTAGAGCAGTGTGGGTACAAAATAAACATGATGCAAGTGTTCATC
ACTGTTTTTGGGAGAATGCCATATCTTTAAGCCGTTAAGAAGAAAAATGATTAAGAA
TAATTTCAAAGTAATGCATGTTTCAAGGGCTAATGCCAGTTGCTCCCAGAGTGGTCTCT
CCCAGTGTCTAGAAATTTTAACTCTTATGAAAATGATATATATGGTCAAAAATGTATTT

FIGURE 15.2

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AACCTTTCCCTTGGCTGCCTTCCAGGGCCAGAGGAAGATCTTCCAAGGAAGATGGAATAC
 TTGGAATTTGTTTGTGTCATGCACCTTCTGAGTATTTCAAGTCACGGTCATCACCATTTCCTC
 ACAGTTCCCACCAGACCAGAGAAGGGCTACATATGGACTCATGTTGGGCCTACTCCTGCA
 ATAACAATTAAGGAATCAGTTGCCAACCATTGTAGTTTCAAAATTAATACTGGGTTTCC
 AGGCCTGGTGTGGTGGCTCACGCCTGTAGCCCCAGCTATTGCACCACTGCTCTCCAAGCT
 GGGCAATGGAGTCAGATTCTCTTTCTTAAAAAACCACAAAAAACTGGATTTCAGTTCT
 CTAATATTCTTAGTACCACAAGATATGTATAGGTATCTTTAAATGAAATTCCTTAGCTGG
 AAAAGTGAATAAAAGTTTTTCTCCTGCTACCTAGTAATAAACAAATCATTGTTTATTAC
 TGGTCACTTAGAAAATTAAGGGGATAGGGCCAGGCACAGTGGCTTATGCCTGTAATTGC
 AGCACTTTTAGAGGCCGAGGCAGGCGGATCACCTGAGGTGCGGAAGTGGATCGCCTGAGG
 TCAGGAGTTCGAGACCAGCCTGGCCAACATGGCGAAACCCGTCGCTACTAAAAATACAA
 AAATTAGCCAGGTGTGGTGGCATGTGCCTGTAATCCCAGCTATTTGGGAGGCTGAGGCAG
 GAGAATCGCCTAAACCCAGGAGGTGGAGGTGTAGTGAGCCAAGATTGCACCGCTGTGCT
 CCAGCCTGGGCAACAGAGTGAGACTCTTGTCTCGGAAAAAAGGCTG
 GGCACAGTGGCTCACGCCTTTAATCCCAGCACTTTGGGAGGCTGAGGCAGATGGATCGCC
 TGAGGTTGGGAGTTCGAGACCAGCCTGGCCAGCATGGTGAAACCCCTGTCTCTACTAAAAA
 TACAAAAATTAGCCAGGTGTGGTGGCGCACACCTGTAGTCCCAGCTACTCGGGAGGCTGA
 GGCAGGAGAATTGGTTGAACCCAGGAGGCGGAGGTTGCAGTGAGCAGAGATCGTGCCACT
 GCACTCCAGCCTGGGTGGACAGAGCAAGACTCCGTCTCAAAGAAACAAACAAAAAATTAA
 AAGGGATAGAATATAATGAAATATATTTGAACTTAAATTATATTCTATATGTGTATCTT
 CCTAGGCAAAAGCTGTAATTTCCAGAGAGACCATTAGGAACAGGTAGTATCTATTTTCT
 CCATTATTTATTTCTAGAACTCATAAAATGGATTGTATTTTCTATAAGAACAAATAT
 TAATTAAGGTATAGATGACTGACCAAGGGCTTAATCAAATAAAATGACTAACAGCATCTA
 TCATAAGCCACACAAGCCTTATGTTCTCATCTCAAAAATGCTGTGACAGCTTTTGGCT
 GCTTTAACCATAAAGAAAAATGATTGGTGATGATTTTATTAGCCAGGCTTTTAAAACT
 TTCATCTAGGCCACGTGCGGTGGCTCATGCCTGTAATCCCGGCACCTTGGGAGGCCTGAG
 TGGATGGATCACTTGAGGTGAGGAGTTCAGGACCAGCCTGGCCAACATGATGAAACCCCTG
 TCTCTACTAAATATACAAAAATTAGTTGGGTGTTATGGTGCATGCCTGTAATCCCAGCTA
 CTCGGGAGGCTGAGGCAGGAGAATTGCTTGAACCTCGGGAGGTGGAGATTGCAGTAAGCCG
 AGATCGTGCCACTGCACTCCAGCCTGGGTGATAGAGCAAGACTGTCTCAAAAAAGAAAA
 AAAGAAAAAATTTAATTTAATCCTTCTGTAGAAACAGGCATTGAGAACCATTCATTGA
 TCTTAATAAAGCTGCTCTTTACTGTTTCTAGTCAAAAATGAGACTTCGATCAAACCATA
 GATTTTATAGTGCAGATAGTCAGCTTACCAAAGCCGAGAGGAAACATGTGAGATCAG
 GCTTCCTGCTTGATAGTCTCTTGACTACCATTAATAACGAATATTGGGAGGTGATGAAAGT
 CATTGGTAGGCCATTAGCATTGATCTTTAAAAACATCTACCCTAAACCATCTGCTATGG
 ACCCATATAAAGAGGCCTGTTGTATATGAAATTGTCTAGAATTCAGGTGCAGGTCTTTGC
 CGGTAAAGTAAGGGAGCAACACGTAAAAATGGGAGAGGAGTGGGGTGTACTCACTTGCCCTC
 CTCTTTTGTCTGATTTAACCCAGCATTTTCAACCCTGGGAAAATTTGCAGAACTAAGT
 TGATTGTAATGATTTTGAGCTGCAGCAGCTTAACTCTTACCCTTTTCCACATAGTTAT
 GGTGTTTGAGTTGGAAAGAAACAACTATAGGTAGCTACACGTACATAATTATCTCTTTAT
 TCACAAAGGGTATAGTAAATTTGATTGTAAATAACTTCTAAGTGCCAATATTCAAACT
 TTTGGATTAAATGTATTTTACCGTGCATTACTTTGGATGTATTTATTTCAATTAA
 CAATTTAAATGGGGCTCTTTAACCAAAAATGGTATTTAAAAACCAAACAGTATCGTACTT
 AGAATTTGGAGTAGAGGCCGGGCACAGTGGCTCACGCCTGTAATCCCAGCACTTTGGAAG
 GCTGAGGCAGGCGGATCACCTGAGGTGAGGAGTTCGAGACCAGCCTGGTCAACATGAAAC
 CCCGTCTCTACTAAAAATACAAAAATTAGCTGGGCGTGGTGGCGTGCCTATAATCCCA
 GCTAGTCTACTCGGGAGGCTGAGGCAGGAGAATCGCTGGAACCTGAGGAGGCAGAGACTGC
 AGTGAGCCGAGATCGCGCCACTGCCTCCAGTCTGGGTGACGGCATGACTCCATCTCCAA
 AAAAAAAGATTTTGGAGTAGATTATCATTAATAAGTAACAGATTTTAGGAAA
 ATCAAAAAATGGCTAATAAAATGAACACAATGTAAACATTTATTAATGTAGACTTTT
 AAAAATCTATAAATTGATCATCTGTTTATAAATTTGGCAGATGGTTGTGTACCATCTTTA
 AAATAAAGATTGAATTTACCCAGTGTGATGGTTCCCATGCTTATTTCTCCTGCTGA

FIGURE 15.3

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GGCCGGACCTGATATGGCCCTGGTCTGTGTTCCCAGCCTTGTTTCCTCATTACCACTAAA
ATCTTTCCCCTGTATGCCGCCCCAATTTTTCTGGCTCTGAGTCCTTGTTTCATACTGTTCT
CTCCAATTCTACCTTCCAAAGGCCTTTCTTAACACCTTCGGATTCTTTCTTTGAGAACTT
TCCAGATTCCCATGCCTTTTTTGGGAATCAATCTCTATCCTATTGTGCATCACATTTAAGTTT
CTACTTCCATCATCCTCACTCCTATCCCTTTGGTCCTGGGATGACAGGGATGCTGTGTTT
TATTTACTCATCTTTGTAACTTCCACATAACCTAACCCCGGTTCTTGCTTATGGGAGATG
CTGATTGTAGGGTCTGAGTTAGATACTGTTAACTAAAAATGCTTGTTGATATTTTAGTTAT
TAATTCATATTAACCTTTGGCTGAACTTTTAAATCTATTGTGAATAGTCAAGTAAATTT
TAGATTGTTACATTCTGGGTTAGTATTAGATTGTTTTTAAGATTGTTTTAAACAAGATGT
TTTTAAGATGAGTTTTAAATAGTTCTCTTAACACAAAATAAGCTTAATATGAGTATTTGA
AGGAAATTATCCCAAACCATCCAGTTCCTGGCTGTGAAAGGCTTTTCCAGGCCATAATA
GTTTTCCACTTCAGCCGTAAGTAGGTGAAATCAAATGAACAATAGAGGGAAATGTATTTA
TTTGCTTTATACACATGTCATGTGTGTTGTGTCTACATATAAACATTGCACACGCTTAGAA
TGAAGTTTCTGTCTATGCCAGAAAAGGGAGAGGCATTTTTGTGGATTTTGTCTGGCTGCC
CTGGGGATGTTTGAAGAACTGTGCTGTTTACTTCATACCAGGTGTGTGAGCCATACCTTT
GGTAGGAGGGTATACCTCCTACACCCAAGAAATATAAGCCAGGAGAAGGTCTGTGCCAAG
AGAAGGAACCCAAATGACCCACAAGAGGTGGGCCATTAAATTATTGGGTGAGATGCATAAA
TGCACAGTAATTTATTTAAGCACCTCTTAATGGTGACCCACAAGGAAGATTGCTCGTAGT
AGCGGAAAGGTTTACAATAAATAAGAGAAAAAGCAGAATGTAGAACTGTATGATAGCAA
TTCTGCAACAAGAAGCATCTTTTATAAAAGATGGAAGGAGCCAGGCACAGTAGCTCAT
GCCTGTAATCCCAGCACTTTAAGAGGCTGAGGTGGAGGATCACTTGAGCTGCAGTGACCC
ATGATTGTGCCACCACTCCAGCCTGGGTGATAGAAGTGAGACCTTCTCTCAAAAAAAAAA
AAAAAAAAAAAAAGACGGAATTCCTCCAGAATTTTAACATGTCAACAGAGGTTTTCTGC
AGCTACTTTTTTTCAGCTTTTATACTTCGCAGTATTTTCCAAATTTTCTCTAACAAGCAGTA
TTTTCCAAATTTTTTACAATAAGCACACACACACACACGTTTGTGTTGCATAAGTGCCC
AACTGGTGGTGAACAACCGCTGGCTTTTAGTCTATACATATCTAGAATATTTTATAAATA
GTAGTTCTTAAACCTTGAAAGGGAGTGAATGACCAGCTGAGAAAATAAAGTCAGTGATT
TCATTATTTTCTATATTCACATCATGATTCTAGGAAAGAACTTGGGAGTGACTTCCTTC
AGCTTCAGCCACTCCTGGGCCAGGCGCATGCTTAGCTCTGTGGTAAAGGTCACCAGCTTC
TTCTGCAGGGTGCTGTATCATGTAATGGAGGTTTGCGGAGGGTAAGAGACTGATGTA
GGTTCAAGTTTTTCTTTCTGTCTCCTCCACTTGAAATCTGTCTTCCCTTCCAGACTGCCTG
CGCTGCTGACTTAAAGCCCCAACACCAAACACAGAAGCAACAGCCTTACACAGAGTGTTT
AGCAAGCTCCAACAATTGTGTAAGGTAAAGTTTCTTTTATAGATTCTTTTCTATATCGC
TCCTAGTGGTCTGTTTCTCTGATCGAATCTGGCTGATAACAGTTGCTGAGACTCTGAA
AGAGAAGGCAAGGAACACTGTTTCTCATTATAAACTGTTTAGAATTATTTGGCCATCTT
TTTGCTATGAATATGTAGTGCTTTGATACATTTTTTAAATCAAAAAGTAATGAAAGAGAT
CACATAGGGAAAGATAGATTGGATTATTTTTTAAAGTTTATATACTAAATTGAAAAGCAAA
GAATAAAATGGGAGAAACAGCTCCCTCATGTGGCTGTTGGCAGGAAGCTTCCATTCTCT
CTGTGGGCCTCCACAGGTTTGCTCACAGCAAATGGTCCGTGACAGAAAGACGCAAGGGCA
GTTGCACCCAAGATGGAAGCCACCATCTTTTCTATAACCTAATCTGAAAGAAGGGACATA
CCAGCACTTCTGCCATATGCTGTTGGGTACACAGACCAACTCTGGTACAGTGTGAACAC
AGGACCACACAAGGGCGTGAATTCAGGGGCAGAGACCACTAGGGACCACTCAGAGGCA
CAGAGGGACACCTATCCAGCTGGTGGCCAATGTAATTAACATAGCTTTTTTAGAATAGC
AATATGTATCTATAATCTTAAAGTATTAAAGTACTTCTTGATCCAGTAATTTTATTTC
TAAGAATCCATGCTAAGAGGATTTAAATGTGGACCAAAAAATGGGTATAAAAAGAAGTT
GTTAACAGTATTTAAAGTTGTGAAAAACCAGAAACAATCTAAAGGTCCAACAATAGGAAA
ATGAATTTTATGATTTTTCTAATAGAATTTTATGCTGTGCATCAGAAATACCATTACAAA
TAATTTTTTAATAACGCAAAAAAAGTTTATAAAATGTTTAGTGTAACCTGGACACAAC
TACATAATGATTCTGATTTTGTAAAAAACAACAAAAACACACATATACACATGCA
TACATATGCATATAAAGAAAACTGGAACAAACAAAATAACAAGCATAGTTGGAATTACAG
TCATTTTAATATCTTTATGCTTTTAAAAATTTTGAAGTTTGTATTACTAGCATCCACTA
CTTACGTAGTCAGGAAAAAATAACAATTTAAATAGATATTTAGGTCCAAAGATGGTAA

FIGURE 15.4

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TCTAAATGGTGTACAGGCTGAATGTGTGCCTGATCCCCATGCCCCAAGTTCATATGTTA
AAGCCCTGGCCCCCAAGGCAATGGTATTAGGGGAGTAGGGCCTTTGGGAGGTAATCAGAT
TTCTACGAGGTCTAGAGGTGGAGCCCGCATAGTGAATTAGTGTCTTTTAGGAAGAGG
AGAACAGACCAAAGCCTTCCTTCTCTCTCACTATGTAAGAAGACAGCCAGAAGGTGGC
CACAGCCAGGAAGAGAGCTCTCACCAGAACCCAAATCTGCTAGCACCTTGCTCTTGGGTT
CTCAGCATCCAGAACTGTGAGAAATGAATGTGTGTTGTTTAAACCACTCAGGCTACGGTA
TTTTGTTGCAGCAGCCCCAAGCTGACAGAGATAGAAACAACACAAGGACCCATCAGCAGAC
GAATGGATGATCAAAACCTGGTGAGGTGCTGTCAGTGGGATATTATTACGCCGTAGAAGGA
ATGAAATTCTGATACATGCTATAATGATGAACCTTGAAAACATGTTAATGGAAATAAGCC
AACTTAAAAGGACAAATATTGTATAATTCCACTTATATGAGTTAGTTACCTAGAATAGG
CAAATTATGTCATAGATACAGAACATTAGAGGTTACCAGGGTTGTGGGAAGAGGGGTATT
GTGGGTACAAATTTTCGGTTTGAGTGTATTTGAAAAAATTCTGGAAATGGGTAGTGACA
GTAGTCAACATGATGAATGTACTTAATGACACTAAATTGTACACTTAAAAATGGTTAATA
CTGGGCTGGCGCAGTGGCTCATGGCTGTAAATCCCAGAACTTTGGGAGGCCAAGACAGGC
GGATCATGAGGTGAGGAGATTGAGACCATTCTGGCTAACATGGTGAACCCCTGTCTCTAC
TAAAAAATAAAAAACAAATAAAAAAATAGCCGGGCATGGTGGCAGGCACCTGTAGTC
CCAGCTACTCGGGAGGCTGAGGCAGGAGAATGGTGTGACCTGGGAGTCGGAGCTTGCAGT
GAGCTGAGATCGCGCCACTGCACTCCAGCCTGGGCAACAGAGCCAGATTCCGTCTCAAAA
AAAAAAGGTTGATACCTGGGTGCGGTGGCTCATGCCTGTAATTTTTCAGCACTTT
GGGAGGCCAAGGCAGGCAGATCAGTTGAGGTCAAGAGTTAAGGACCAGCCTGGCCAACGT
GGCGAAACCCCATCTCTATTAAAAATACAAAAATTAGTCGAGTGTGGTGGTGGTGCCTG
TAGTCCCAGCTGCTGGGAGGATGAGGCCTAGGAATTGCTTGAACCCAGGAGGCAGAGGTT
GCAGTGAGTTGAGATTGCGCCACTGCACTCCAGCCTGGGGGACAGAGCGAGACTTAGTCT
CAAAAAAAGGTTAAATTTGTAAGTTTGTATGTCATATTTTACCATAATCTTTAAAAAA
TAGATATATAGGAGATAAAGTCAACAGAATTTAATAACCAAGTTGTAAATAGAGACTGAGT
GAGGAGGATGAATTAAGGAAGACATTGAGTACAACCTTTTGGTAGGTGAAAACTCTTAA
AAAAATACGTGGGCAAGATCCTACTTGATTCTTATAATTTAAAAATCTCCAGTTAGTA
ACAAGGCTAGGTGGAGATTGTCATGTGATGTGAGGTGTGTGTTCTGTTTTGTAATGTGA
GGACTGTGAGCCATCTCCTGGACTTGAATATCCATTAGATAATTGAAAAACGGATTGTA
GAACTCAGGAGACGTGCAATGCAGTAACAAACTCTGCACCTAGTTGATTTCTGTCTCCT
AATTTAATGCTTTTATGGGACAAACTGTTAGGCAGGTGGGCAAGATGGACAGCCATATTT
TTGTGGGTTTCTGGCCTGTGGGCCAGCCTCAGTGCTCACTCTGAGGTGATGTCCAACTT
AGAACACATTGAGCCTACCACAGTCAAGGCTCCCTTTCTCAACTCTAGTCTCTGCACA
AATATCCGAAGCCTAGAAATAATAATCATCTGTCTCTGTGCTTGCATTATGAAAGCCTA
GGAAAGGGCCTTGGGAATTAAAGAAGATGGAAAAAAGTCTAAGTGTGCTGCTTCTCAG
CTTGACAGGGGAATCACTGAAATGGGGACAGGCCATAAAAGGACAACCAGAAGAGTGGCTT
CAGCAAAGGCATCGTTTTTTCAGAGCAAGCTAGAGAATCCTGCCAGCGTCTCAGGCAGGG
CCCCTGGGCACAGAGGTTAGGCAAGGGAGTGTCCAGCATGTTGATGCCCTGAGCATCAG
AATAATGCCATAGAGGAGCTTCCAAAGAGTTTCAATTCAGGTTTTGTAGCCGAACATTTT
TAGGCAAATAAAATTTGATTTTGTGAATAAAGCTTGTCTTCAACTCCAGTGCAGATTC
TCATAGATTGATAGTGGCTTGTGATCCAGATAAAGAAAAACAATTTTTCAAAGATTCATAT
TCTTTGTAGATGTACGGATTTAGAGACCATCTAATCTAACTCCCTCATTCTACAGATAGG
AAAAATGAGGCCTAAAGAAGTTAAGAAAATACCATGGAAATGTCACTGCTGAAGTGCAT
ACGTAGGATCCGAAAGAAATTTGGGTAAATGCTACTGTGAGAAATACAGTACTAGGTCCAA
AGAATCTAATACAAATTAATAATCTAATGTTATTTCTAAAGCATCCCTGCACATGGCTG
AACTTACATAGTTTCAATTTCTTTCTTTCTGTTGAAGAAGAGGCAATTGGCTGGGTGCA
GTGGCTCATGCCGTGAATCCTGGCACTTTGAGAGGCCGAGGCGGGTGGATCACCTGAGGT
CAGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCCATCTCTACTAAAAATACAAA
AATTAGCTGGCTGTGGTGGCCGCTGCCTGTAATCCCAGCTACTCCAGAGGCTGAGGCAGG
AGAATTACTTGAATCTGGGAGGTGGAGGTTGCAGTGAGCCAAGATCACGCCATTGCACTC
TAGCCTGGATGACAAGAGGGAACTCCATCTCAAAAAAAGAAAAAAGCAATCACT
AACCTGTGTTGTTTATTAAACATGACAGACTGGCATGAAGTAATTACCAACTGTAAACA

FIGURE 15.5

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AAAAAGCTACAATCTGCCAGGCATGGTGGCTCATGCCTGTAATCCCCACCTTGGGAGGC
CAGGTTGGGGGATCACCTGAGGCCTGGAGTTCAAGACTAGCCTGGTCAACATGGTGAAAC
CTCGTCTCTACTAAAAATACAAAAATTAGCCCGCGTGGTGGCACATCCCTGTAATCCCA
GTTACTCAGGAGGCTGAGGCAGGAGAATCACTTGAACCTGGGCAGTGGGGAGGTTGCAGT
GAGCCAAGATCGCACCGTTGTACTCCAGTCTGGGCCGACAGAGTGAGACTCGGTCTCAAA
AAAAAGAAAAAGAAAAAGCTACAACCTTAATCTCAACTTCTCATAACATCATCTCTACTT
CTGATTAGAAGAGTGGAAAGTGGGGAGGTTTATTACAAAAAGACTGTTATACCTTACACAC
TTCTCCCCATGAATAGTGAAGGTGTGAGTGAAAAAGACAGCAATTTTATTTTTTTTTTGA
AACAGGTTCTTGCACGTGCACCCGGGCTGGAGTGCACCTGTTGTGATCACTGCTCACTGCA
GCCTCCACCTCCCAGGCTCAAGTGATCCTCCTACCTCAGCCTCCTGAGTAGCTGGGACCA
CAGTTGTGCACTACCATGCCCAGCTATTTTTTTTTTAAGAGATGGGGTCTCACTATATTGC
TTAGGCTAGTTCTCAAACCTCCTGGCCTCAAGCAGTCCTCCGACCTTGGCCTCCCAAAGGG
TTGTGATTACAGGCATAAGCCACCACACCCAGCCAGCAGTTTTAGAATAAAGGGTGAAGG
TGCTGTTGGGGAAATATAATTTAAAAAACAAATCTTCTCTCAACCCAGAAATCCTCTCC
ATGAAGGCAGTAGAGAAAGATAAGCTTTATTATTGAATAAAAAATTAAATGAGAATGTGAT
GCACATCACAGGCACTTTTGCTAAGAGATCACAAGACAGAAGGAAATTCACCATTTTGT
ACAGCCAAGCAGGTACAGCCCATTACATGTATGTTTTTCGAGATAAATAGTCCTCAACTAA
GAGAACTTGACAGCACCCTGGTCACACAGTTCATTCTAACTTTACCTGATAATTGATGT
GACCACTTGTGTTATCTAAGATATCAACTTTTTCGGGGGTGGGGGAGTGTGGAAACAGGAG
TTACTTTTTATAGCTTGGTGCAAGGTACTCATTAAGATTAGGCTGTTACCCTCCCACAGAA
ACTGGAAGATAGGTATGCTATCTGGTAATGTTTACATTTCCAGATCCTTGAGAAAGACA
TTCTAGGTCATAAAGCTGACAAAAGGCTGATTCAGTTTTTAAATATATATATCTGTATA
TGTATTTCA

FIGURE 15.6

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actgagagacaggactagctggatttcctaggctgactaagaatccctaagcctagctgg
|||||
actgagagacaggactagctggatttcaggccgactaagaattcctaagcctagctgg

g-aaggtgaccacatccacctttaaacacggggcttgcaacttagctcacacctgaccaa
|||||
ggaaggtgaccacacctcctttaaacacagagcttgtaactcagctcacaccgaccaa

tcag-----agagctcactaaaatgctaattaggc-aaagacaggaggtaaagaaa
|||||
tcaggtagtaaagagagctcactaaaataccaattaggctaaaaacaggaggtaaagaaa

tagccaa-tcatctattgcctgagagcacagcaggagggacaatgatcgggatataaacc
|| |||
taatcaaatacatctatcgctgagagcacagggggagggacaatgatcgggatataaacc

caagtcttcgagccggcaacggcaacccccctttgggtccctccctttgtatgggagctc
|| | |||
caggcatttgagccagatcaggtaacctcctttgggtccctccactgtatgggagctc

tggtttcatgctatttcactctattaaatcttgcaactgcac--tcttctgggtccatggt
|||||
tggt-----ttactctattaaatcttgcaactgcacactcttctgggtccatggt

tcttaagggttgagctgagctttcgctcgccatccaccactgctggttgccgccaccgca
|| |||
tggtccgggtcaagctgagcttttgctcgccgtccaccactgctgaatgcgccattgca

gaccgcgcgctgactcccatccctctggatcatgcagggtgtccgctgtgctcctgatcc
|||||
gacctgcccttgacttcacccctccggatccggcagagtgctccgctgcaactcctgatcc

agcgaggcacccattgccgctcccaatcgggctaaaggcttgccattggttctgcatggc
|||||
agcgaggcacccattgccactcccgatcaggctaaaggcttgccattggttctgacagc

taagtgcctgggttcacctaattgagctgaacactagtcactgggttccatgggttctct
|||||
taagtgcctgggttcacctaatacaggctgaacactgggtcgctgggttccacgggttctct

tctgtgacccacagcttctaataagagctataaacactcaccgcatggcccaagggttcatt
|| |||
tccatgactcacagcttctaataagagctataaacactcaccacatggcccaagggttcatt

cctt-gaatccataaggccaagaaccccagggtcagagaacacgaggcttgccaccatctt
|| |||
cgttggaatccatgaggccaagaaccccagggtcagagaataaaaggcccgcc-ccatctt

gggag
|||||
gggag

FIGURE 16

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TCCTGTGAAC CTCTAGAGGA TTTGCGCCTG CTCTTCAAAC AACAAACCAGG AGGAAAGTAA 7860
CTAAATCAT AAATCCCCAT GGCCCTCCT TATCATATTT TTCTCTTAC TGTTCTTTTA 7920
CCCTCTTTCA CTCTCACTGC ACCCCCTCCA TGCCGCTGTA TGACCAGTAG CTCCCCTTAC 7980
CAAGAGTTTC TATGGAGAAT GCAGCGTCCC GGAAATATTG ATGCCCATC GSTATAGGAGT 8040
CTTTCTAAGG GAACCCCCAC CTTCACTGCC CACACCCATA TGCCCCGCA CTGCTATCAC 8100
TCTGCCACTC TTTGCATGCA TGCAAATACT CATTATTGGA CAGGAAAAAT GATTAATCCT 8160
AGTTGTCTG GAGGACTTGG AGTCACTGTC TGTGGACTT ACTTCACCCA AACTGGTATG 8220
TCTGATGGG GTGGAGTTCA AGATCAGGCA AGAGAAAAAC ATGTAAAAGA AGTAATCTCC 8280
CAACTCACC GGGTACATGG CACCTCTAGC CCCTACAAAG GACTAGATCT CTCAAACTA 8340
CATGAAACCC TCCGTACCCA TACTCGCCTG GTAAGCCTAT TTAATACCAC CCTCACTGGG 8400
CTCCATGAGG TCTCGGCCCA AAACCCTACT AACTGTTGGA TATGCCTCCC CCTGAACTTC 8460
AGGCCATATG TTTCAATCCC TGTACCTGAA CAATGGAACA ACTTCAGCAC AGAAATAAAC 8520
ACCACTTCCG TTTTAGTAGG ACCTCTGT TCCAATCTGG AAATAACCCA TACCTCAAAC 8580
CTCACCTGTG TAAAATTTAG CAATACTACA TACACAACCA ACTCCCAATG CATCAGGTGG 8640
GTAACCTCTC CCACACAAT AGTCTGCCTA CCCTCAGGAA TATTTTTTGT CTGTGGTACC 8700
TCAGCCTATC GTTGTTTGAA TGGCTCTTCA GAATCTATGT GCTTCCTCTC ATTCTTAGTG 8760
CCCCCTATGA CCATCTACAC TGAACAAGAT TTATACAGTT ATGTCATATC TAAGCCCCGC 8820
AACAAAAGAG TACCCATTCT TCCTTTTGTT ATAGGAGCAG GAGTGCTAGG TGCACTAGGT 8880
ACTGGCATTG GCGGTATCAC AACCTCTACT CAGTTCTACT ACAAACTATC TCAAGAACTA 8940
AATGGGGACA TGGAAACGGGT CGCCGACTCC CTGGTCACCT TGCAAGATCA ACTTAACTCC 9000
CTAGCAGCAG TAGTCCTTCA AAATCGAAGA GCTTTAGACT TGCTAACCGC TGAAAGAGGG 9060
GGAACCTGTT TATTTTTAGG GGAAGAATGC TGTATTATG TTAATCAATC CGGAATCGTC 9120
ACTGAGAAAG TTAAAGAAAT TCGAGATCGA ATACAACGTA GAGCAGAGGA GCTTCGAAAC 9180
ACTGGACCTT GGGGCCTCCT CAGCCAATGG ATGCCCTGGA TTCTCCCTT CTTAGGACCT 9240
CTAGCAGCTA TAATATTGCT ACTCCTCTT GGACCCTGTA TCTTTAACT CTTGTTAAC 9300
TTTGTCTCTT CCAGAATCGA AGCTGTAAAA CTACAAATGG AGCCCAAGAT GCAGTCCAG 9360
ACTAAGATCT ACCGCAGACC CCTGGACCGG CTGCTAGCC CACGATCTGA TGTTAATGAC 9420
ATCAAAGGCA CCCCTCCTGA GGAAATCTCA GCTGCACAAC CTCTACTAG CCCCATTCA 9480
GCAGGAAGCA GTTAGAGCGG TCTCGGCCAA CCTCCCCAAC AGCACTTAGG TTTTCCTGTT 9540

FIGURE 17

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AAGCTCCTTCAGGAGAACAAAGAACAGGCCATTACCCTGGAGAAGACTGGCAACTGATTTTACCCACAAGCCCAA
LysLeuLeuGlnGluAsnLysGluGlnAlaIleThrLeuGluLysThrGlyAsn...PheTyrProGlnAlaGln
SerSerPheArgArgThrLysAsnArgProLeuProTrpArgArgLeuAlaThrAspPheThrHisLysProLys
AlaProSerGlyGluGlnArgThrGlyHisTyrProGlyGluAspTrpGlnLeuIleLeuProThrSerProAsn

ACCTCAGGGATTTCAGTATCTACTAGTCTGGGTAGATACTTTACGGGTTGGGCAGAGGCCTTCCCCTGTAGGAC
ThrSerGlyIleSerValSerThrSerLeuGlyArgTyrPheHisGlyLeuGlyArgGlyLeuProLeu...Asp
ProGlnGlyPheGlnTyrLeuLeuValTrpValAspThrPheThrGlyTrpAlaGluAlaPheProCysArgThr
LeuArgAspPheSerIleTyr...SerGly...IleLeuSerArgValGlyGlnArgProSerProValGlyGln

AGAAAAGGCCCAAGAGGTAATAAAGGCACTAGTTCATGAAATAATTCCCAGATTCCGGACTTCCCCGAGGCTTACA
ArgLysGlyProArgGlyAsnLysGlyThrSerSer...AsnAsnSerGlnIleArgThrSerProArgLeuThr
GluLysAlaGlnGluValIleLysAlaLeuValHisGluIleIleProArgPheGlyLeuProArgGlyLeuGln
LysArgProLysArg.....ArgHis...PheMETLys...PheProAspSerAspPheProGluAlaTyrArg

GAGTGACAATAGCCCTGCTTTCCAGGCCACAGTAACCCAGGGAGTATCCCAGGCGTTAGGTATACGATATCACTT
Glu...Gln...ProCysPheProGlyHisSerAsnProGlySerIleProGlyValArgTyrThrIleSerLeu
SerAspAsnSerProAlaPheGlnAlaThrValThrGlnGlyValSerGlnAlaLeuGlyIleArgTyrHisLeu
ValThrIleAlaLeuLeuSerArgProGln...ProArgGluTyrProArgArg...ValTyrAspIleThrTyr

ACACTGCGCCTGAAGGCCACAGTCCTCAGGGAAGGTCGAGAAAATGAATGAAACACTCAAAGGACATCTAAAAA
ThrLeuArgLeuLysAlaThrValLeuArgGluGlyArgGluAsnGlu...AsnThrGlnArgThrSerLysLys
HisCysAla...ArgProGlnSerSerGlyLysValGluLysMETAsnGluThrLeuLysGlyHisLeuLysLys
ThrAlaProGluGlyHisSerProGlnGlyArgSerArgLys...METLysHisSerLysAspIle...LysSer

GCAAACCCAGGAAACCCACCTCACATGGCCTGCTCTGTTGCCTATAGCCTTAAAAAGAATCTGCAACTTTCCCCA
385 395 405 415 425 435 445
AlaAsnProGlyAsnProProHisMETAlaCysSerValAlaTyrSerLeuLysLysAsnLeuGlnLeuSerPro
GlnThrGlnGluThrHisLeuThrTrpProAlaLeuLeuProIleAlaLeuLysArgIleCysAsnPheProGln
LysProArgLysProThrSerHisGlyLeuLeuCysCysLeu...Pro...LysGluSerAlaThrPheProLys

AAAAGCAGGACTTAGCCCATACGAAATGCTGTATGGAAGGCCCTTCATAACCAATGACCTTGTGCTTGACCCAAG
LysSerArgThr...ProIleArgAsnAlaValTrpLysAlaLeuHisAsnGln...ProCysAla...ProLys
LysAlaGlyLeuSerProTyrGluMETLeuTyrGlyArgProPheIleThrAsnAspLeuValLeuAspProArg
LysGlnAspLeuAlaHisThrLysCysCysMETGluGlyProSer...ProMETThrLeuCysLeuThrGlnAsp

ACAGCCAACTTAGTTGCAGACATCACCTCCTTAGCCAAATATCAACAAGTTCTTAAACATTACAAGGAACCTAT
ThrAlaAsnLeuValAlaAspIleThrSerLeuAlaLysTyrGlnGlnValLeuLysThrLeuGlnGlyThrTyr
GlnProThr...LeuGlnThrSerProPro...ProAsnIleAsnLysPheLeuLysHisTyrLysGluProIle
SerGlnLeuSerCysArgHisHisLeuLeuSerGlnIleSerThrSerSer...AsnIleThrArgAsnLeuSer

CCCTGAGAAGAGGGAAAAAGAACTATTCCACCCTTGACATGGTATTAGTCAAGTCCCTTCCCTCTAATTCCCCA
Pro...GluGluGlyLysGluLeuPheHisProCysAspMETValLeuValLysSerLeuProSerAsnSerPro
ProGluLysArgGluLysAsnTyrSerThrLeuValThrTrpTyr...SerSerProPheProLeuIleProHis
LeuArgArgGlyLysArgThrIleProProLeu...HisGlyIleSerGlnValProSerLeu...PheProIle

TCCCTAGATACATCCTGGGAAGGACCCTACCCAGTCATTTTATCTACCCCAACTGCGGTTAAAGTGGCTGGAGTG
SerLeuAspThrSerTrpGluGlyProTyrProValIleLeuSerThrProThrAlaValLysValAlaGlyVal
Pro...IleHisProGlyLysAspProThrGlnSerPheTyrLeuProGlnLeuArgLeuLysTrpLeuGluTrp
ProArgTyrIleLeuGlyArgThrLeuProSerHisPheIleTyrProAsnCysGly...SerGlyTrpSerGly

FIGURE 18.1

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GAGTCTTGGATACATCACACTTGAGTCAAATCCTGGATACTGCCAAAGGAACCTGAAAATCCAGGAGACAACGCT
 GluSerTrpIleHisHisThr...ValLysSerTrpIleLeuProLysGluProGluAsnProGlyAspAsnAla
 SerLeuGlyTyrIleThrLeuGluSerAsnProGlyTyrCysGlnArgAsnLeuLysIleGlnGluThrThrLeu
 ValLeuAspThrSerHisLeuSerGlnIleLeuAspThrAlaLysGlyThr...LysSerArgArgGlnArg...

AGCTATTCTGTGAACCTCTAGAGGATTTGCGCCTGCTCTTCAAACAACAACCAGGAGGAAAGTAACTAAAATCA
 SerTyrSerCysGluProLeuGluAspLeuArgLeuLeuPheLysGlnGlnProGlyGlyLys...LeuLysSer
 AlaIleProValAsnLeu...ArgIleCysAlaCysSerSerAsnAsnAsnGlnGluGluSerAsn...AsnHis
 LeuPheLeu...ThrSerArgGlyPheAlaProAlaLeuGlnThrThrThrArgArgLysValThrLysIleIle

TAAATCCCCATGGCCCTCCCTTATCATATTTTTCTCTTTACTGTCTTTTACCCTCTTTCACTCTCACTGCACCC
 ...IleProMETAlaLeuProTyrHisIlePheLeuPheThrValLeuLeuProSerPheThrLeuThrAlaPro
 LysSerProTrpProSerLeuIleIlePhePheSerLeuLeuPhePheTyrProLeuSerLeuSerHisPro
 AsnProHisGlyProProLeuSerTyrPheSerLeuTyrCysSerPheThrLeuPheHisSerHisCysThrPro

CCTCCATGCCGCTGTATGACCAGTAGCTCCCCTTACCAAGAGTTTCTATGGAGAATGCAGCGTCCCGGAAATATT
ProProCysArgCysMETThrSerSerSerProTyrGlnGluPheLeuTrpArgMETGlnArgProGlyAsnIle
 LeuHisAlaAlaVal...ProValAlaProLeuThrLysSerPheTyrGlyGluCysSerValProGluIleLeu
 SerMETProLeuTyrAspGln...LeuProLeuProArgValSerMETGluAsnAlaAlaSerArgLysTyr...

GATGCCCCATCGTATAGGAGTCTTTCTAAGGGAACCCCCACCTTCACTGCCCACACCCATATGCCCCGCAACTGC
AspAlaProSerTyrArgSerLeuSerLysGlyThrProThrPheThrAlaHisThrHisMETProArgAsnCys
 METProHisArgIleGlyValPheLeuArgGluProProProSerLeuProThrProIleCysProAlaThrAla
 CysProIleVal...GluSerPhe...GlyAsnProHisLeuHisCysProHisProTyrAlaProGlnLeuLeu

TATCACTCTGCCACTCTTTCATGCATGCAAATACTCATTATTGGACAGGAAAAATGATTAATCCTAGTTGTCCT
TyrHisSerAlaThrLeuCysMETHisAlaAsnThrHisTyrTrpThrGlyLysMETIleAsnProSerCysPro
 IleThrLeuProLeuPheAlaCysMETGlnIleLeuIleIleGlyGlnGluLys...LeuIleLeuValValLeu
 SerLeuCysHisSerLeuHisAlaCysLysTyrSerLeuLeuAspArgLysAsnAsp...Ser...LeuSerTrp

GGAGGACTTGGAGTCACTGTCTGTTGGACTTACTTCACCCAAACCTGGTATGTCTGATGGGGGTGGAGTTCAAGAT
GlyGlyLeuGlyValThrValCysTrpThrTyrPheThrGlnThrGlyMETSerAspGlyGlyGlyValGlnAsp
 GluAspLeuGluSerLeuSerValGlyLeuThrSerProLysLeuValCysLeuMETGlyValGluPheLysIle
 ArgThrTrpSerHisCysLeuLeuAspLeuLeuHisProAsnTrpTyrVal...TrpGlyTrpSerSerArgSer

CAGGCAAGAGAAAAACATGTAAAAGAAGTAATCTCCCAACTCACCCGGGTACATGGCACCTCTAGCCCCTACAAA
GlnAlaArgGluLysHisValLysGluValIleSerGlnLeuThrArgValHisGlyThrSerSerProTyrLys
 ArgGlnGluLysAsnMET...LysLys...SerProAsnSerProGlyTyrMETAlaProLeuAlaProThrLys
 GlyLysArgLysThrCysLysArgSerAsnLeuProThrHisProGlyThrTrpHisLeu...ProLeuGlnArg

GGACTAGATCTCTCAAAACTACATGAAACCTCCGTACCCATACTCGCCTGGTAAGCCTATTTAATACCACCCTC
GlyLeuAspLeuSerLysLeuHisGluThrLeuArgThrHisThrArgLeuValSerLeuPheAsnThrThrLeu
 Asp...IleSerGlnAsnTyrMETLysProSerValProIleLeuAlaTrp...AlaTyrLeuIleProProSer
 ThrArgSerLeuLysThrThr...AsnProProTyrProTyrSerProGlyLysProIle...TyrHisProHis

ACTGGGCTCCATGAGGTCTCGGCCCAAAACCTACTAACTGTTGGATATGCCTCCCCCTGAACTTCAGGCCATAT
ThrGlyLeuHisGluValSerAlaGlnAsnProThrAsnCysTrpIleCysLeuProLeuAsnPheArgProTyr
 LeuGlySerMETArgSerArgProLysThrLeuLeuThrValGlyTyrAlaSerPro...ThrSerGlyHisMET
 TrpAlaPro...GlyLeuGlyProLysProTyr...LeuLeuAspMETProProProGluLeuGlnAlaIleCys

GTTTCAATCCCTGTACCTGAACAATGGAACAACTTCAGCACAGAAATAAACACCACTTCCGTTTGTAGTAGACCT
ValSerIleProValProGluGlnTrpAsnAsnPheSerThrGluIleAsnThrThrSerValLeuValGlyPro
 PheGlnSerLeuTyrLeuAsnAsnGlyThrThrSerAlaGlnLys...ThrProLeuProPhe.....AspLeu
 PheAsnProCysThr...ThrMETGluGlnLeuGlnHisArgAsnLysHisHisPheArgPheSerArgThrSer

FIGURE 18.2

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CTGTGTTTCCAATCTGGAAATAACCCATACCTCAAACCTCACCTGTGTAAAATTTAGCAATACTACATACACAACC
LeuValSerAsnLeuGluIleThrHisThrSerAsnLeuThrCysValLysPheSerAsnThrThrTyrThrThr
 LeuPheProIleTrpLys...ProIleProGlnThrSerProVal...AsnLeuAlaIleLeuHisThrGlnPro
 CysPheGlnSerGlyAsnAsnProTyrLeuLysProHisLeuCysLysIle...GlnTyrTyrIleHisAsnGln

AACTCCCAATGCATCAGGTGGGTAACCTCCACACAAATAGTCTGCCTACCCTCAGGAATATTTTTTGTCTGT
AsnSerGlnCysIleArgTrpValThrProProThrGlnIleValCysLeuProSerGlyIlePhePheValCys
 ThrProAsnAlaSerGlyGly...LeuLeuProHisLys...SerAlaTyrProGlnGluTyrPheLeuSerVal
 LeuProMETHisGlnValGlyAsnSerSerHisThrAsnSerLeuProThrLeuArgAsnIlePheCysLeuTrp

GGTACCTCAGCCTATCGTTGTTTGAATGGCTCTTCAGAATCTATGTGCTTCCTCTCATTCTTAGTGCCCCCTATG
GlyThrSerAlaTyrArgCysLeuAsnGlySerSerGluSerMETCysPheLeuSerPheLeuValProProMET
 ValProGlnProIleValVal...METAlaLeuGlnAsnLeuCysAlaSerSerHisSer...CysProLeu...
 TyrLeuSerLeuSerLeuPheGluTrpLeuPheArgIleTyrValLeuProLeuIleLeuSerAlaProTyrAsp

ACCATCTACACTGAACAAGATTTATACAGTTATGTCATATCTAAGCCCCGCAACAAAAGAGTACCCATTCTTCCT
ThrIleTyrThrGluGlnAspLeuTyrSerTyrValIleSerLysProArgAsnLysArgValProIleLeuPro
 ProSerThrLeuAsnLysIleTyrThrValMETSerTyrLeuSerProAlaThrLysGluTyrProPhePheLeu
 HisLeuHis...ThrArgPheIleGlnLeuCysHisIle...AlaProGlnGlnLysSerThrHisSerSerPhe

TTTGTATAGGAGCAGGAGTGCTAGGTGCACTAGGTACTGGCATTGGCGGTATCACAACTCTACTCAGTTCTAC
PheValIleGlyAlaGlyValLeuGlyAlaLeuGlyThrGlyIleGlyGlyIleThrThrSerThrGlnPheTyr
 LeuLeu...GluGlnGluCys...ValHis...ValLeuAlaLeuAlaValSerGlnProLeuLeuSerSerThr
 CysTyrArgSerArgSerAlaArgCysThrArgTyrTrpHisTrpArgTyrHisAsnLeuTyrSerValLeuLeu

TACAACTATCTCAAGAACTAAATGGGGACATGGAACGGGTGCGCGACTCCCTGGTCACCTTGCAAGATCAACTT
TyrLysLeuSerGlnGluLeuAsnGlyAspMETGluArgValAlaAspSerLeuValThrLeuGlnAspGlnLeu
 ThrAsnTyrLeuLysAsn...METGlyThrTrpAsnGlySerProThrProTrpSerProCysLysIleAsnLeu
 GlnThrIleSerArgThrLysTrpGlyHisGlyThrGlyArgArgLeuProGlyHisLeuAlaArgSerThr...

AACTCCCTAGCAGCAGTAGTCCCTTCAAAATCGAAGAGCTTTAGACTTGCTAACCGCTGAAAGAGGGGGAACCTGT
AsnSerLeuAlaAlaValValLeuGlnAsnArgArgAlaLeuAspLeuLeuThrAlaGluArgGlyGlyThrCys
 ThrPro...GlnGln...SerPheLysIleGluGluLeu...ThrCys...ProLeuLysGluGlyGluProVal
 LeuProSerSerSerSerProSerLysSerLysSerPheArgLeuAlaAsnArg...LysArgGlyAsnLeuPhe

TTATTTTTAGGGGAAGAATGCTGTTATTATGTTAATCAATCCGGAATCGTCACTGAGAAAGTTAAAGAAATTCGA
LeuPheLeuGlyGluGluCysCysTyrTyrValAsnGlnSerGlyIleValThrGluLysValLysGluIleArg
 TyrPhe...GlyLysAsnAlaValIleMETLeuIleAsnProGluSerSerLeuArgLysLeuLysLysPheGlu
 IlePheArgGlyArgMETLeuLeuLeuCys...SerIleArgAsnArgHis...GluSer...ArgAsnSerArg

GATCGAATACAACGTAGAGCAGAGGAGCTTCGAAACACTGGACCCTGGGGCCTCCTCAGCCAATGGATGCCCTGG
AspArgIleGlnArgArgAlaGluGluLeuArgAsnThrGlyProTrpGlyLeuLeuSerGlnTrpMETProTrp
 IleGluTyrAsnValGluGlnArgSerPheGluThrLeuAspProGlyAlaSerSerAlaAsnGlyCysProGly
 SerAsnThrThr...SerArgGlyAlaSerLysHisTrpThrLeuGlyProProGlnProMETAspAlaLeuAsp

ATTCTCCCCTTCTTAGGACCTCTAGCAGCTATAATATTGCTACTCCTCTTTGGACCCTGTATCTTTAACCTCCTT
IleLeuProPheLeuGlyProLeuAlaAlaIleIleLeuLeuLeuLeuPheGlyProCysIlePheAsnLeuLeu
 PheSerProSer...AspLeu...GlnLeu...TyrCysTyrSerSerLeuAspProValSerLeuThrSerLeu
 SerProLeuLeuArgThrSerSerSerTyrAsnIleAlaThrProLeuTrpThrLeuTyrLeu...ProProCys

FIGURE 18.3

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GTAACTTTGTCTCTTCCAGAATCGAAGCTGTAAACTACAAATGGAGCCCAAGATGCAGTCCAAGACTAAGATC
ValAsnPheValSerSerArgIleGluAlaValLysLeuGlnMETGluProLysMETGlnSerLysThrLvsIle
LeuThrLeuSerLeuProGluSerLysLeu...AsnTyrLysTrpSerProArgCysSerProArgLeuArgSer
...LeuCysLeuPheGlnAsnArgSerCysLysThrThrAsnGlyAlaGlnAspAlaValGlnAsp...AspLeu

TACCGCAGACCCCTGGACCGGCCTGCTAGCCACGATCTGATGTTAATGACATCAAAGGCACCCCTCCTGAGGAA
TyrArgArgProLeuAspArgProAlaSerProArgSerAspValAsnAspIleLvsGlyThrProProGluGlu
ThrAlaAspProTrpThrGlyLeuLeuAlaHisAspLeuMETLeuMETThrSerLysAlaProLeuLeuArgLys
ProGlnThrProGlyProAlaCys...ProThrIle...Cys.....HisGlnArgHisProSer...GlyAsn

ATCTCAGCTGCACAACCTCTACTACGCCCCAATTCAGCAGGAAGCAGTTAGAGCGGTCGTCGGCCAACCTCCCCA
IleSerAlaAlaGlnProLeuLeuArgProAsnSerAlaGlvSerSer...SerGlyArgArgProThrSerPro
SerGlnLeuHisAsnLeuTyrTyrAlaProIleGlnGlnGluAlaValArgAlaValValGlyGlnProProGln
LeuSerCysThrThrSerThrThrProGlnPheSerArgLysGlnLeuGluArgSerSerAlaAsnLeuProAsn

ACAGCACTTAGGTTTTCTGTTGAGATGGGGG
ThrAlaLeuArgPheSerCys...AspGlyGly
GlnHisLeuGlyPheProValGluMETGly
SerThr...ValPheLeuLeuArgTrpGly

FIGURE 18.4

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LysLeuLeuGlnGluAsnLysGluGlnAlaIleThrLeuGluLysThrGlyAsn...PheTyrProGlnAlaGln
ThrSerGlyIleSerValSerThrSerLeuGlyArgTyrPheHisGlyLeuGlyArgGlyLeuProLeu...Asp
ArgLysGlyProArgGlyAsnLysGlyThrSerSer...AsnAsnSerGlnIleArgThrSerProArgLeuThr
Glu...Gln...ProCysPheProGlyHisSerAsnProGlySerIleProGlyValArgTyrThrIleSerLeu
ThrLeuArgLeuLysAlaThrValLeuArgGluGlyArgGluAsnGlu...AsnThrGlnArgThrSerLysLys

AlaAsnProGlyAsnProProHisMETAlaCysSerValAlaTyrSerLeuLysLysAsnLeuGlnLeuSerPro
LysSerArgThr...ProIleArgAsnAlaValTrpLysAlaLeuHisAsnGln...ProCysAla...ProLys
ThrAlaAsnLeuValAlaAspIleThrSerLeuAlaLysTyrGlnGlnValLeuLysThrLeuGlnGlyThrTyr
Pro...GluGluGlyLysGluLeuPheHisProCysAspMETValLeuValLysSerLeuProSerAsnSerPro
SerLeuAspThrSerTrpGluGlyProTyrProValIleLeuSerThrProThrAlaValLysValAlaGlyVal
GluSerTrpIleHisHisThr...ValLysSerTrpIleLeuProLysGluProGluAsnProGlyAspAsnAla
SerTyrSerCysGluProLeuGluAspLeuArgLeuLeuPheLysGlnGlnProGlyGlyLys...LeuLysSer
...IleProMETAlaLeuProTyrHisIlePheLeuPheThrValLeuLeuProSerPheThrLeuThrAlaPro
ProProCysArgCysMETThrSerSerSerProTyrGlnGluPheLeuTrpArgMETGlnArgProGlyAsnIle
AspAlaProSerTyrArgSerLeuSerLysGlyThrProThrPheThrAlaHisThrHisMETProArgAsnCys
TyrHisSerAlaThrLeuCysMETHisAlaAsnThrHisTyrTrpThrGlyLysMETIleAsnProSerCysPro
GlyGlyLeuGlyValThrValCysTrpThrTyrPheThrGlnThrGlyMETSerAspGlyGlyGlyValGlnAsp
GlnAlaArgGluLysHisValLysGluValIleSerGlnLeuThrArgValHisGlyThrSerSerProTyrLys
GlyLeuAspLeuSerLysLeuHisGluThrLeuArgThrHisThrArgLeuValSerLeuPheAsnThrThrLeu
ThrGlyLeuHisGluValSerAlaGlnAsnProThrAsnCysTrpIleCysLeuProLeuAsnPheArgProTyr
ValSerIleProValProGluGlnTrpAsnAsnPheSerThrGluIleAsnThrThrSerValLeuValGlyPro
LeuValSerAsnLeuGluIleThrHisThrSerAsnLeuThrCysValLysPheSerAsnThrThrTyrThrThr
AsnSerGlnCysIleArgTrpValThrProProThrGlnIleValCysLeuProSerGlyIlePhePheValCys
GlyThrSerAlaTyrArgCysLeuAsnGlySerSerGluSerMETCysPheLeuSerPheLeuValProProMET
ThrIleTyrThrGluGlnAspLeuTyrSerTyrValIleSerLysProArgAsnLysArgValProIleLeuPro
PheValIleGlyAlaGlyValLeuGlyAlaLeuGlyThrGlyIleGlyGlyIleThrThrSerThrGlnPheTyr
TyrLysLeuSerGlnGluLeuAsnGlyAspMETGluArgValAlaAspSerLeuValThrLeuGlnAspGlnLeu

FIGURE 19.1

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AsnSerLeuAlaAlaValValLeuGlnAsnArgArgAlaLeuAspLeuLeuThrAlaGluArgGlyGlyThrCys
LeuPheLeuGlyGluGluCysCysTyrTyrValAsnGlnSerGlyIleValThrGluLysValLysGluIleArg
AspArgIleGlnArgArgAlaGluGluLeuArgAsnThrGlyProTrpGlyLeuLeuSerGlnTrpMETProTrp
IleLeuProPheLeuGlyProLeuAlaAlaIleIleLeuLeuLeuLeuPheGlyProCysIlePheAsnLeuLeu
ValAsnPheValSerSerArgIleGluAlaValLysLeuGlnMETGluProLysMETGlnSerLysThrLysIle
TyrArgArgProLeuAspArgProAlaSerProArgSerAspValAsnAspIleLysGlyThrProProGluGlu
IleSerAlaAlaGlnProLeuLeuArgProAsnSerAlaGlySerSer...SerGlyArgArgProThrSerPro
ThrAlaLeuArgPheSerCys...AspGlyGly

FIGURE 19.209719554-011001
FIG 19.2

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SerSerPheArgArgThrLysAsnArgProLeuProTrpArgArgLeuAlaThrAspPheThrHisLysProLys
ProGlnGlyPheGlnTyrLeuLeuValTrpValAspThrPheThrGlyTrpAlaGluAlaPheProCysArgThr
GluLysAlaGlnGluValIleLysAlaLeuValHisGluIleIleProArgPheGlyLeuProArgGlyLeuGln
SerAspAsnSerProAlaPheGlnAlaThrValThrGlnGlyValSerGlnAlaLeuGlyIleArgTyrHisLeu
HisCysAla...ArgProGlnSerSerGlyLysValGluLysMETAsnGluThrLeuLysGlyHisLeuLysLys
GlnThrGlnGluThrHisLeuThrTrpProAlaLeuLeuProIleAlaLeuLysArgIleCysAsnPneProGln
LysAlaGlyLeuSerProTyrGluMETLeuTyrGlyArgProPheIleThrAsnAspLeuValLeuAspProArg
GlnProThr...LeuGlnThrSerProPro...ProAsnIleAsnLysPheLeuLysHisTyrLysGluProIle
ProGluLysArgGluLysAsnTyrSerThrLeuValThrTrpTyr...SerSerProPheProLeuIleProHis
Pro...IleHisProGlyLysAspProThrGlnSerPheTyrLeuProGlnLeuArgLeuLysTrpLeuGluTrp
SerLeuGlyTyrIleThrLeuGluSerAsnProGlyTyrCysGlnArgAsnLeuLysIleGlnGluThrThrLeu
AlaIleProValAsnLeu...ArgIleCysAlaCysSerSerAsnAsnAsnGlnGluGluSerAsn...AsnHis
LysSerProTrpProSerLeuIleIlePhePheSerLeuLeuPhePheTyrProLeuSerLeuSerLeuHisPro
LeuHisAlaAlaVal...ProValAlaProLeuThrLysSerPheTyrGlyGluCysSerValProGluIleLeu
METProHisArgIleGlyValPheLeuArgGluProProProSerLeuProThrProIleCysProAlaThrAla
IleThrLeuProLeuPheAlaCysMETGlnIleLeuIleIleGlyGlnGluLys...LeuIleLeuValValLeu
GluAspLeuGluSerLeuSerValGlyLeuThrSerProLysLeuValCysLeuMETGlyValGluPheLysIle
ArgGlnGluLysAsnMET...LysLys...SerProAsnSerProGlyTyrMETAlaProLeuAlaProThrLys
Asp...IleSerGlnAsnTyrMETLysProSerValProIleLeuAlaTrp...AlaTyrLeuIleProProSer
LeuGlySerMETArgSerArgProLysThrLeuLeuThrValGlyTyrAlaSerPro...ThrSerGlyHisMET
PheGlnSerLeuTyrLeuAsnAsnGlyThrThrSerAlaGlnLys...ThrProLeuProPhe.....AspLeu
LeuPheProIleTrpLys...ProIleProGlnThrSerProVal...AsnLeuAlaIleLeuHisThrGlnPro
ThrProAsnAlaSerGlyGly...LeuLeuProHisLys...SerAlaTyrProGlnGluTyrPheLeuSerVal
ValProGlnProIleValVal...METAlaLeuGlnAsnLeuCysAlaSerSerHisSer...CysProLeu...
ProSerThrLeuAsnLysIleTyrThrValMETSerTyrLeuSerProAlaThrLysGluTyrProPhePheLeu
LeuLeu...GluGlnGluCys...ValHis...ValLeuAlaLeuAlaValSerGlnProLeuLeuSerSerThr
ThrAsnTyrLeuLysAsn...METGlyThrTrpAsnGlySerProThrProTrpSerProCysLysIleAsnLeu
ThrPro...GlnGln...SerPheLysIleGluGluLeu...ThrCys...ProLeuLysGluGlyGluProVal

FIGURE 20.1

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TyrPhe...GlyLysAsnAlaValIleMETLeuIleAsnProGluSerSerLeuArgLysLeuLysLysPheGlu
IleGluTyrAsnValGluGlnArgSerPheGluThrLeuAspProGlyAlaSerSerAlaAsnGlyCysProGly
PheSerProSer...AspLeu...GlnLeu...TyrCysTyrSerSerLeuAspProValSerLeuThrSerLeu
LeuThrLeuSerLeuProGluSerLysLeu...AsnTyrLysTrpSerProArgCysSerProArgLeuArgSer
ThrAlaAspProTrpThrGlyLeuLeuAlaHisAspLeuMETLeuMETThrSerLysAlaProLeuLeuArgLys
SerGlnLeuHisAsnLeuTyrTyrAlaProIleGlnGlnGluAlaValArgAlaValValGlyGlnProProGln
GlnHisLeuGlyPheProValGluMETGly

FIGURE 20.209719554-01801
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AlaProSerGlyGluGlnArgThrGlyHisTyrProGlyGluAspTrpGlnLeuIleLeuProThrSerProAsn
LeuArgAspPheSerIleTyr...SerGly...IleLeuSerArgValGlyGlnArgProSerProValGlyGln
LysArgProLysArg.....ArgHis...PheMETLys...PheProAspSerAspPheProGluAlaTyrArg
ValThrIleAlaLeuLeuSerArgProGln...ProArgGluTyrProArgArg...ValTyrAspIleThrTyr
ThrAlaProGluGlyHisSerProGlnGlyArgSerArgLys...METLysHisSerLysAspIle...LysSer
LysProArgLysProThrSerHisGlyLeuLeuCysCysLeu...Pro...LysGluSerAlaThrPheProLys
LysGlnAspLeuAlaHisThrLysCysCysMETGluGlyProSer...ProMETThrLeuCysLeuThrGlnAsp
SerGlnLeuSerCysArgHisHisLeuLeuSerGlnIleSerThrSerSer...AsnIleThrArgAsnLeuSer
LeuArgArgGlyLysArgThrIleProProLeu...HisGlyIleSerGlnValProSerLeu...PheProIle
ProArgTyrIleLeuGlyArgThrLeuProSerHisPheIleTyrProAsnCysGly...SerGlyTrpSerGly
ValLeuAspThrSerHisLeuSerGlnIleLeuAspThrAlaLysGlyThr...LysSerArgArgGlnArg...
LeuPheLeu...ThrSerArgGlyPheAlaProAlaLeuGlnThrThrThrArgArgLysValThrLysIleIle
AsnProHisGlyProProLeuSerTyrPheSerLeuTyrCysSerPheThrLeuPheHisSerHisCysThrPro
SerMETProLeuTyrAspGln...LeuProLeuProArgValSerMETGluAsnAlaAlaSerArgLysTyr...
CysProIleVal...GluSerPhe...GlyAsnProHisLeuHisCysProHisProTyrAlaProGlnLeuLeu
SerLeuCysHisSerLeuHisAlaCysLysTyrSerLeuLeuAspArgLysAsnAsp...Ser...LeuSerTrp
ArgThrTrpSerHisCysLeuLeuAspLeuLeuHisProAsnTrpTyrVal...TrpGlyTrpSerSerArgSer
GlyLysArgLysThrCysLysArgSerAsnLeuProThrHisProGlyThrTrpHisLeu...ProLeuGlnArg
ThrArgSerLeuLysThrThr...AsnProProTyrProTyrSerProGlyLysProIle...TyrHisProHis
TrpAlaPro...GlyLeuGlyProLysProTyr...LeuLeuAspMETProProProGluLeuGlnAlaIleCys
PheAsnProCysThr...ThrMETGluGlnLeuGlnHisArgAsnLysHisHisPheArgPheSerArgThrSer
CysPheGlnSerGlyAsnAsnProTyrLeuLysProHisLeuCysLysIle...GlnTyrTyrIleHisAsnGln
LeuProMETHisGlnValGlyAsnSerSerHisThrAsnSerLeuProThrLeuArgAsnIlePheCysLeuTrp
TyrLeuSerLeuSerLeuPheGluTrpLeuPheArgIleTyrValLeuProLeuIleLeuSerAlaProTyrAsp
HisLeuHis...ThrArgPheIleGlnLeuCysHisIle...AlaProGlnGlnLysSerThrHisSerSerPhe
CysTyrArgSerArgSerAlaArgCysThrArgTyrTrpHisTrpArgTyrHisAsnLeuTyrSerValLeuLeu
GlnThrIleSerArgThrLysTrpGlyHisGlyThrGlyArgArgLeuProGlyHisLeuAlaArgSerThr...
LeuProSerSerSerSerProSerLysSerLysSerPheArgLeuAlaAsnArg...LysArgGlyAsnLeuPhe

FIGURE 21.1

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IlePheArgGlyArgMETLeuLeuLeuCys...SerIleArgAsnArgHis...GluSer...ArgAsnSerArg
SerAsnThrThr...SerArgGlyAlaSerLysHisTrpThrLeuGlyProProGlnProMETAspAlaLeuAsp
SerProLeuLeuArgThrSerSerSerTyrAsnIleAlaThrProLeuTrpThrLeuTyrLeu...ProProCys
...LeuCysLeuPheGlnAsnArgSerCysLysThrThrAsnGlyAlaGlnAspAlaValGlnAsp...AspLeu
ProGlnThrProGlyProAlaCys...ProThrIle...Cys.....HisGlnArgHisProSer...GlyAsn
LeuSerCysThrThrSerThrThrProGlnPheSerArgLysGlnLeuGluArgSerSerAlaAsnLeuProAsn
SerThr...ValPheLeuLeuArgTrpGly

FIGURE 21.209/719554-01501
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TTGGTCTTAAGAACACAAATGATATGGCTCCAATGACTGGAGGAACACCAGGGTCCTTGG
TCTCACGCTGATTTAGATAAAACGACTGTCTAGGCCTCTGAGCCCAAGCTAAGCCATCCTC
CCCTGTGACCTGCACGTATACATCCAGATGGCCTGAAGTAACCAAAGAATCACAAAAGCA
GTGAAAAATGGCCTGTTCTGCCTTAACTGATGACATTCCACCATTGTGATTTGTTCTGC
CCCATCTTAACTGAGCGATTAACCTTGTGAAATTCTTCTCCTGGCTCAAAACCTCCCCC
ACTGAGCACCTTGTGACCCCCGCCCCCTGCCCTAAGAGAAAAACCCCTTTGATTATAATT
TTCCACTACCCACCCAAATCCTATAAAATGGCCCCACCCCTATCTCCCTTCGCTGACTCC
TTTTTCGGACTCAGCCCGCCTGCACCCAGGTGAAATAAACAGCCTTGTGCTCACACAAA
GCCTGTTTGGTGGACTCTCTTCACACGACGCTCATGACATTTGGTGCCAAAACCTGGGA
TAGGAGGACTCCTTCAGGAGACCAGTCCCCTGTCTTGGCCTCACTCTGTGAGGACATCC
ACCTACAACCTTGGGTCTCAGACCAACCAGCCCAAGGAACAGCTCACCAATTTCAAATC
AGGTAAGCAGTCTTTTCACTCTCTTCTCCAGCCTCTCTTGCTACCCTTCAAACCTCCCTCT
CTCACTACCCTTCAATCTCCCTGTCTTCCAATTCCAGTTCTTTTTCATCTCTAGTAGAG
ACAAAGGAGACACATTTTATCCATGGACCCAAAACCTCCAGCACCAGTCACGGACTTGGGA
AGACAGTCTTCCCTTGGTGTTTAATCACTGCGGGGACGCCTGCCTGATTATTCACCCACA
CTCCATTGGTGTCTGATCAGGTTGGGGACACCTGCCTTGGTCACTCACCCACATTCCCTT
GGTGGTACGTCAACTGCAAAAGCAGGGGACGCCTGCTTTGGCTGCTCACCCACCCCTTC
TCTGTGTCTCTACCTTTCTCTTTAAACTTACCTCCTTCACTATGGGCAAACCTTCTGCCCT
CCATTCCCCCTTCTTCTCCCTTAGCCTGTGTTCTTAAAAACCTAAAACCTCTTCAACTCA
CACCTGACCTAAAACCTAAATGCCTTATTTTCTTCTGCAACACTGCGTGGCTGCAGTACA
AACTTGATAATAGCTTTAAATGGCCAGAATATGGCACTTTCAATTTCTCCATCCTACAAG
ATCTAGATAATTTTGTGGAAAAATGGAATAATGGTCTGAGATGCCTGACGTCCAGGCAT
TCTTTTACACATTGGTCCCTCCCTAGTCTCTGCTCCCAATGCGACTCATCCCAAATCTTT
CTTCTTTCTCTCCTGTCTGTTCTTCTCAGTCTCCACCCCAAGCTCTGAGTCTTTGAATCC
TCCTTTGCTACAGACCCATCTGAACTCTCCCCTCCTCCCCAGGCTGCTCCTCACCAGGCC
GAGCCAGGTCCCAATTCTTCTCAGCCTCTGCTCCCCCACCCTATAATCCTTTTATCACC
TCCTCTCCTCACACTCAGTCCGGCTTACAGTTTCTGTTCTGTGACTAGCCCTCCCCATCT
GCCCAACAATTTCTTAAAGAGGTGGCTGGAGCTAAAGGCATAGTCAAGGTTAATGCT
CCTTTTCTTTATCTGACCTCTCCCAAATCAGTTAGCGTTTACGCTCTTTTTCATCAAAT
ATAAAAACCCAGCCAGTTTATGCCCCATCTGGCAACAACCTTACAGGCTTTACAGCCCT
AGACCCTGAAGGGTCAAGAGGCCGTCTTATTCTCAATATGCATTTTATTACCCAATCCGC
TCCCAACATTAAATAAAGCTCCAAAAATTAAATTCTGGCCCTCAAACCCCAACAGGAC
TTAATTAACCTCACTTCAAGGTGTACAAGAATAGAGTAGAGGCAGCCAAGTAGCAACGTA
TTTGAGTTGCAATTCCTTGCCTCAACTCTGAGAGAAACCCAGCCACATCTCCAGCAAAAC
AAGAACTTCAAAACACCTGAACTGCAGCAGCCAGGCGTTCTCCAGGACCACCTCCCCCA
GGATCTTGCTTCAAGTGCCGGAATCTGACCATTGGGCAAGGAATGCCTGCAGCCAGG
ATTCCTCCTAAGCCACGTCCCATTTGTGACAGGACCCCACTGGAAATCGGACTGTCCAAT
CACCCGGCAGCCAATCCCAGAGCCCCTGGAACCTCTGGCCCAAGGCTCTCTGACTGACTCC
TTCCCAGATCTTCTCGGCTTAGCAGCTGAAGACTGACACTGCCCCGATCACTTCAGAAGTC
CCCTGGACCATCACGGATACTGAGCTTCAGGTAACCTCTCACAGTGGAGGCTAAGTCCATC
CCCTGTTTAAATCGATACAGGGGCTACCCACTCCACATCACCTTCTTTTCAAGGGCCTGTT
TCCCTTTCCCCCATAACTGTTGTGGGTATTGACGGCCAAGCTTCAAACCCCTTAAACT
CCCCCACTCTGGTGCCAACTTGGACAACATTCTTTTATGCACTCTTTTTCAGTTATCCTC
ACCTGCCCAGTTCCCTTATTAGGCCGAGACATTTTAAACCAATTATCTGCTTCCCCGACT
ATTCTGGGGCTACAGCCACATCTCCTTGCCGCCCTTCTTCCCAACCCAAAGCCTCCTTCA
TATCTTCTCTCATATCCCCCACCCTTAAACCAAGTATGGGACACCTCTACTCCCTCC
CTGGCAACCGATCACACGCCCATTAATATCCCATTAATAACCTAATCACCTTACCCTGCT
CAATGCCAGTATCCCATACCACAACAGGCTTTAAAGGGATTGAAGCCTGTTATCACTTGC

FIGURE 22.1

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CTGCTACAGCACGGGCTTCTAAAACCTATAAACTCTCCATACAATTCCCCCATTTTACCT
GTCTAAAAACCAGATAAGTCTTACAGGTTAGTTCAGAATCTGCACCTTATCAACCAAATT
GTTTTGCCTATCCACCCTGTAGCACCCAACTCGTACACTCTTTTGTCTCAATGCCTTCC
CCCACAACCTCACTATTCCGTTCTTGATCTTAAAGATGCTTTTTTCACTATTCCCTGCAC
CCCTCATCCCAGCCTCTCTTTGCTTTTACCTGGACTGACCCTGACACCCATCAGTCCAG
CAGCTTACCTGGGCTGTACTGCCGCAAGGCTTCAGGGACAGCCCTCATTACTTCAGCCAA
GCTCTTTCTCATGATTACTTTCTTTCCACCTCTCTGCTTCTCACCTTATTCAATATATT
GATGACCTTCTACTTTGTAGCCCTCCTTTAAATCTTCTCAACAAGACACCCCTCCTGCTC
CTTCAACATTTGTTCTCCAAAGGATATCGGGTATCCCCCTCCAAAGCTCAAATTTCTTCT
CCATCTGTTACATACCTCGGCATAATTCTTCATGAAAACACATGTGCTCTCCCTGCCAAT
TGCGTCTCCAACCTGATCTCTCAAATCCCAACCTCTTCTACAAAACAACAACTCCTTTCCC
TCCTAGGCATGGTTGGATACTTTTGCTTTGGATACTGGTTTTGCCATCCTAACAAAAT
CATTATATAAACTCACAAAAGGAAACCTAGCTGACCCCATAGATTCTAAATCCTTTCCCC
ACTCCTCTTTCCATTCTTGAAGACAGCTTTAGAGACTGCTCCCACTAGCTCTCCCTG
TCTCATCCCAACCCTTTTCATTACACACAGCCGAAGTGCAGGGCTGTGCAGTCGGAATTC
TTACACAAGGACCGGGACCATGCCCTGTAGCCTTTTTGTCCAAACAACCTTGACCTTACTG
TTTTAGGCTCGCCATCATGTCTCCATGCGGTAGCTTCCGCTGCCCTAATACTTTTAGAGG
CCCTCAAAATCACAACTATGCTCAACTCACTCTCTACAGCTCTCACAACTTCCAAAATC
TATTTTCTTTCTCACACCTGACGCATATACTTTCTGCTCCCCGGCTCCTTCAGCTGTATT
CACTCTTTGTTGAGTCTCCCACAATTACCATTTCTTCTGCGCCAGACTTCAATCTGGCCT
CCCACATTATTCTGGATACCACACCTGACCCTGATGATTGTATGTCTCTGATCTACCTGA
CATTACCCCATTTCCCATATTTCTTCTTTTCTGTTCTCTCATGTTGATCACATTTGGT
TTACTGACGGCAGTTCCACCAGGCTGATCGCCACTCACCAGCAAAGGCAGGCTATGCTA
TAGAATCTTCCACATCCATCATTGAGGCTACTGCTCTGCCCCCTCCACTACCTCTCAGC
AAGCCGAACCTGATTGCCTTAACTCGGGCCTTCACTCTTGCAAAGGGACTACACGTCAATA
TTTATACTGACTCTAAATATGCCTTCCATATCTTGCAACCACCATGCTGTTATATGGGCTG
AAAGAGGTTTCTCACTACGCAAGGGTCTCCATCATTAAATGCCTCTTTAATAAAAACTC
TTCTCAAGGCTGCTTTACTTCCAAAGGAAGCTGGAGTCACACACTGCAAGGGCCACCAAA
AGGCGTCAGATCCCATTACTCTAGGAAATGCTTATGCTGATAAGGTAGCTAAAGAAGCAC
CTAGCGTTCCAACCTTCTGTCCCTCATGGCCAGTTTTTCTCCTTCCCATCAGTCATTCCCA
CCTACTCCCCCATTTGAAACTTCCGCTATCAATCTCTTCTCACACAAGGCAAAATGGTTCT
TAGACCAAGGAAAATATCTCCTTCCAGCCTCACAGGCCCATTTCTATTCTGTATCATTTT
ATAACCTCTTCCATGTAGGTTACAAGCCACTAGTCCACCTCTTAGAACCTCTCATTTCCT
TCCATCGTGGAACATATCCTCAAGGAAATCACTTCTCAGTGTTCCATCTGCTATTCTAC
TACCCCTCAGGGATTGTTAGGCCCCCTCCCTCCCTACACATCAAGCTCGGGGATTTGC
CCCTGCCCAGGACTGGCAAATTGACTTTACTCACATGCCCTGAGTCAGGAAACTAAAATA
CCTCTTGGTCTGGGTAGACACTGTCACTGGATGGGTAGAGGCCCTTTCCACAGGGTCTGA
GAAGGCCACTGCAGTCATTTCTTCCCTTCTGTGAGACATAATTCCTTGGGTGTCCTTCC
CACCTCTATACAGTCCAATAACGGAGCAGCCTTTATTAGTCAAATCACCTGAGCAGTTTT
TCAGGCTCTTGGTATTGAGTGAACCTTCGTACCCCTTACTGTCTCAATCTTCAGGAAA
GGTAGAATGGACTAATGGTCTTTTAAAAACACACCCCAACAACTCAGCCTCCAACCTTAA
AAAGGAGGATAGAGCCCAAAACTCGCAACCAAGCTAGTAATTATGCTGAACCCCTTGG
GCACTCTCTAATTGGATGTCTTAGGTCCTCCCAAATCTTAGTCCTTTAATATCTGTTTTT
CTCCTTCTCTTATTTCGGACCTTGTGTCTTCCGTTTAGTTTTTCAATTCATACAAAACCGC
ATCCAGGCCATCACCAATCGTTCTATACAATAAATGCTCCTTCTAACAACCCCAACATAT
CGCCCCCTTACCACAAAATCTTCCCTCAGCTTAATCTCTCCCACTCTAGGTTCCCATGCCG
CCCATAATCCCTCTCGAAGCAGCCCTGAGAAACATAGCCCATATCTCTCCATACCACCC
CCAAAATTTTTGCTGCCCCAACACTTCAACACTATTTTACATTATTTTCTTATTAATAT

FIGURE 22.2

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AAGAAGACAGCAATGTCAGGCCTCTGAGCCCAAGCCATCATATCCCCTGTGACCTGCACA
TATACATCCAGATGGCCTGAAGTAACTGAAGAATCACAAAAGAGTGAAAATGGCCTGTT
CCTGCCTTAACCGATGACATTCCACCCTGTGATTTGTTCCCTGCCCCACCTTAACTGAGC
AATTAACCTTGGGAAATTCCTTCTCCTGGCTCAAAACCTCCCCACTGAGCACCTTGTGA
CCCCTGCCCCCTCCACTACCCACCCAAATCCTATAAAATGGCCCCACCCCATCTCCCTTAG
CTGACTCCTTTTTTGGACTCAGCCCGCCTGCACCCAGGTGAAATAAACAGCCTTGTTGCT
CACACAAAGCCTGTTTGGTGGACTCTCTTCACAGGGACGGGGGTGACAACAACACGGACA
CACATGGAGTGGTTTTAAGGAGCAGAGATTTAATACGCAAAAAAGAAGGAAGAGGCTCC
CCTGTACAGACACAGAGGGAGGGGGCTCCAAGCCGAGAGAAGGAAACCCCATGTGCAGTG
GAAAAGTGGTTGATTATACTGGGAGGCTGGAGGAGGCGGTGTCTGATTTGCACAGGGCCC
AGGGGATTGGGTTGACCAGGTGTATCATTATGTACCCCGCAAAAAACCTGGCCCTCCCA
CCTCAGCCCTTTAATATGCAAATGTGGGTTGCCATGATGTTCTGAAAACACATGAATTAT
CTGGAGGGGGCCATGACACTTGGTACATGTGCTGACAAGAAGAGGGTGGAATCGCCATG
GTGGCCATGTTGGGTGGACCTAGTTTTTAATAGCCTGCATTTGCATATCAAAGTTTGCTG
GCCTGGCTCTTTAAGCTGTCTTTCTGTGTAGAAAAGGAATGGTTTGGAATGGGTGAGGGT
TGCTTCTTATTACAAGAAAAATTTCCAAAAACCTTTACTCTTTCTAGCTGCCAAAAAACTA
TTTCTTAATAACTTATGTATTACCATAATTAGGCAGCACCAAAGATCCCTGCAGGTCAGA
CCACTGCAATTAACATGCTGGCTTTACTGCTGATTATGGTAGCTGCATCCACCTAGCCTC
TCATATTGCAACTGCCTGACCTCTGCCACCCACGAGCCACTTATCCCCACTTATAATCA
GCCCATTTTCGATTGTAACATCTGCCACTTATTCCCGACGTTGTGGTATATCCTATAGATG
AATTCATTCAACATCCATTCCAACACCACCTCTCTTGCCCTTCCTATACTCTCTGGAGAGT
GAATTACTGAGTCACATGATCTTCACTGCAGTCATTTGTGGCTATGTGACATAGTTCTGG
ACAGTGAACATAGACAGAAGTCCCTGGGGCGGGCTTCCTTTCTGGGATGAGGGCAAAACG

FIGURE 22.3

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GATCTCTTGATCCCAGGAGGTCAAGGCTGCAATGAGCTAAGATCAAGCCACTGCATTCCA
GCCTGAGTGATAGTGGGAGACCTTGCTCTTTAAACACACACACACACACACACACACG
AGGGCCTTTGACCCTCTTGAGTAGAAGACTCGAGAAGAAACAAAGTAGAAGGCCAGAGAA
GAACAAAGTTACTTGAAAGATCTCTTATTAAAGAGAATGTACAAGCTATGAAAAAAAAA
AACACACACACACACACAAACCTCATCTGGAATGAAAAAACATAATGCATTTGGTTTCT
GGTTCCTTAGGCTGTTATGGAACAACCAAGAACATTATTTGGTTTCTGAGGTCAGAAC
TATTTTATCCCTCAAGCACACTATGCTTATGGTTTGAGGGAGAATGAGAAATAGGAAA
CTAGGAACAGGCTGAAATGGTCTAATCTTGACCATCTAATTCTGCAGTGTCTTATTCTCA
TTCTAAAAGAGAATGGTTATATTGCGTGTCTAGCATAAAAAAGTAATGATAAAAAATAAAA
GATCCCGTATTACCAGACAATAATCCCTAGACTGTTTTAATGCTTGGTTGAGTATTTGC
TTATGATCTCAGACTTTAAAAGATGGTCTCCCCCTATGGTGAAGCTTGTTAATTATGTAG
GCATCATTAATGTCTGTTTACTTATCAAAATTTTATCATTGTTAGTTGTATTACTACTTG
ACAGTCCAATTTATTTAATTGAAAAGATTGGTTAACATTTTATAGTCAAAGTAATTGTTT
CCTGTGTTTTTTTCTGTTTAGGTTATTGGAGTGATGAGTAAAGAATACATACCAAAGGGC
ACACGTTTTGGACCCCTAATAGGTGAAATCTACACCAATGACACAGTTTCCTAAGAACGCC
AACAGGAAATATTTTTGGAGGGTAAGTAAGGGAAATTTCTTCAGACCCATTAAATGTTAG
GAAAAATGGAGCTAAAAGAGCTGGGTGGCTCACCTTTCTCATCCTGTGCTGAGAAATGC
TGGGGCTCACCCATAAGTATCCAGCATCCCCATGGACACAGGGAATTCGAAACAAATGTG
ATGAAACCGATGAAATGTCTGGCCTGTAGGTGGTTAGTGATGGAGATACGGGCTATATGT
GAATCTTGATTTTTGCAATTCATTAGAGCTTTGTAATGAAAGGAAACAGTTTGTTGCTTG
CTTTAAGGATAGGTTCAATTTGCATTTCTCCGCAAGGAAGTAGTAATGAGTTACCAAGCCT
TAGATTTACCCCTTTTTGATTTCTTGCTGACTTAACCTTTAATTGAATGGAAGAGTTATC
ACAAATGAATTATCTTTTTGGTTTTTTTTTTTTTTGAGATGGAGTCTCACTCTGTCAACAG
GCTGGAGTGCAATGGCATGATCTCGGCTCACTGCAACCTCCGCCTCCAGGTTCAAGCAA
TTGTCCTGCCTCAGCCTCCCGAGTAGCTGGGACTAAGGTGCGCGCCACCATGCCAGTTA
ATTTTTGTATTTTTAGTAGAGACGGGGTTCCACTATGTTGGCCATGATGGTCTCGATCTC
TGGACCTCGTGATCCGCCACCTTGCCCTCCCAAAGTGCTGGAATTACAGGCAAGAGCCA
CCGCGCCAGCCAGGAATGACAAATGAATTACCTTATAAGTAAATGCCATTAAAGGAAGGA
TAGCTGGAAGATGGGTTGAGGGGAATGGAGGACCACAGAACTAGTCCTATTTAAATACAT
GTGCATGGTAAATGATTCCATTTGACAATAGGTTAATTATCTCATAGCATAAGGAAAAT
GCTTAACAGTCAATGCAAGATGATAAGCTTTCTATAGCATCCAACCAAAGATCTAGC
CAGTACAATTTCTTTGCTATATTAGGGTTAGAAAGGCCCCAGAGGTGAACCAATTAGA
TGGAATCCTTGAATAAAACACTGGATTAGCAGTGAACAGAAAAAGTCAGATTGCTTTCC
TTCTTCCCATAGATGTCTCAGGGATATTTAGTTTTCTCAGAAGATAAAGAATTTAGTAAG
CGTTTTTTTTGTGCATACTTACATGAAATGTACATTATTTGAATTTCTTTAAAAAGAAACAG
CTGCATGATAACAAAAATTGTGTTATGCTTGCTTTAGCTGGTATTTTTGCCTAGAACGAT
TATATCGTTCCGACAAGAAGCTATTCCCTAAGAAACAATATTTTTAATCCAGGAAGTTTTT
CATTTTTAGAAATTTATCTTACTATTTCCCAAGCAAAAGAGGGTAGTTACAGATTCACCTA
AGAATCATGTGCTCACAATTTTTATTTAATAATTATTCTCCTTAAATATATTAATCAC
CTGACTTACAATGGTGAACCATGAGTGCATTTTTGCCTTTATTGTCAATAACGTCTTCT
CAGAAGTGAGCCACAAAGGTGCATAGTTCTTGAGTTAAAGGTCTGAATTAAGACAATCC
AGCATAAGTCTCATTAAATGTGTGATTATTTGAGAAAAGGCAAGAAGTACCTAAGAATCT
CCCCCTCACTGTCCAGTTCCCTGTTTCATTTAAAGATTCACTGTAAGTAACTGAAAGGCT
TTCTTTGGGAGGATTTATTTGAATCAGTCTTTCACATGCAAAGGATATTGTAGAACATCT
CGTTTTTGTCTGGCAGGAATATGAACATCTGTTGTGAGGAAAGAAAAAGTTTCATGCAAT
TACACTGCCAAAGAAGGGATGTTCAAGTTGAGAAACAGTGACATTTCTTGTAACGTGAC
TATGAATCAGCGCATTTTAAATCTCTAGATAATATATGGAAGTGCAGGAAGGTGGTAGGA
AACGGTGTTCAATTTACATATGCGTTATTTTATTCTGTGTGAGTGAATTCATGGCACCGA
CATTGCTGTTTTTAAATGAGGATACAGTAAATGCAGTCCGAGGAAGGCTAACTGGAATC
AACATACCCGTAGCTTTAGAAAGCAGTTTCCGCAACGAGCAAGAGTACAAGAGCGATGGA
ACCCCATGTTCTTGGAAGTTTGCACATCAGAGTAAACAACTTGAAAACCCCTCTTGATA

FIGURE 23.1

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GCAGAATTACCCAGCCTTGTTCCATTTTCTCTTAACAAAACACACCGCAAAGCTCTCA
CAAGCTGCTTTGATGAAGCCACATGTATTTCCCCCTTCACAATTTACAGGAAGTTACTCT
TAAAAGAAAGTGATTCTGGTGTAAACCGCTGTGTTAAAGGGACAGAGTTCCTTTTTATT
TCTGATAACGTTTGAGCGAAATACAGAACTATCTGTAGACTAGCATAGTCGGTACGTGA
GTAAGGAAAAGCAATAACCTGCTGTCCGGTGAGCACAAAATTCTGCTACGAACAGTGCC
TTACTGCTGCTTGGAGACTGCAAGTCGCAGATCACACTAGGTATTGACTGATTGTATAAG
GAAATTTCTTAAAGTCTAAAGTAAAGGTGGTACCTCCTAAAAAGAGGGGAAGAGAGAAAA
CTTGTGTGGAAGGATAAGGAGTGTGTTTATAGTTTCAGTAAGAGTGTACGTTTTAATTT
TTCTTCTTCTCTGCCTCTTTGCCAAGTAGCCTGAGTGCATCTGTTATCCAGAAGTAGTA
TTACTCTAGGACAAACTTCAAATCTTTCATTCTGCGTTGCCTTTAAGGAACAACATACTT
TCTTCTGTTCTTTTTCCAAAACACACGCCTATGGCTCTGTGTGTGGTGTGTTTAGCCAG
CCTCCTCCAGATAAGGGGTTCCCTTCCCTCCTTTGCATTGAAAGGAAAGTGCAAGTCTG
GACATGTTTATCAAGAGGAAAAGTGACTTCTCAGTAATAGACTGTCAAATTCGGGCTGCT
GCCCCAGTGTTTCGCTTTGTTATGGCAGGTGAAGTTCACCTTTGCCCCACCCAGTGTTC
ACAAAAGGCAAGGTTCCAAGTATTCATATGAACAAGTGTACTTTAGGACTTGGAGGGT
TGGGGGTGGAGGATGTTTGCATAGTTGAAGCCTTGGGCGGGGGTGTAGGAAACGGCGAGT
ACAGAGGCCATAGAAAAAGCTAAGACTCAGTTTGACGTTCGTGAGCCGGCTTGGTCTTCTA
CCCAGTGACTCAAAGCACTAAAAGTCAGCATAATCGGAACTGAAGTCAGTAGCATCGCCC
ATTTGCCATTCACTGCAGTAGCAAAAGTAGTACTCTGTGGTGGGTTAATCGGTTTGAGGC
AGCTCCTTAAATGAACATTTGTGTTTCATTTTTCTGTTATTTTCCCGAATGAAAAGAC
GATAAACTGAAATGGAAGGTAAGTGCACAAAAGTGTGCCTTACCTGTTTCCGCCCTGA
TTTCTGCTGATTCAAGACTATTCTGGCTAAACTGATTGGATTCTTTTTCTAACTAGGCAG
TAGGGGATCAGAAATCACACACGGTACCGGCTGTGTTTATTCTGAGAGGTGCTGGGGAGC
TTTGGGTCTGACTTCCTTTTACATGCCTGTCTTCTCTTTGGACAGATCTATTCCAGAGG
GGAGCTTCACTTTCATTGACGGCTTTAATGAAGAGAAAAGCAACTGGATGCGCTATGT
GAATCCAGCACACTCTCCCCGGGAGCAAAACCTGGCTGCGTGTGAGAACGGGATGAACAT
CTACTTCTACACCATTAAGCCCATCCCTGCCAACCCAGGAACTTCTTGTGTGGTATTGTG
GGACTTTGCAGAAAGGCTTCACTACCTTATCCCGGAGAGCTGACAATGATGAATCTCAG
TAAGTGGATTACAGAACAAAAAATAAAAAATGCCAGTAATGTGCGTTCTGCCCCTTTGA
ACTAATAACATGTTGTTTAAATTATACGGCTTTGTGATGTGTTGGATGAAGTAGGTGGCTT
AAGCTAGGGACTAGGAAGAGGAAAAACATTTTTTGTAGTCCCTATTAATCTATTAGGAACT
TGATCATTTAAAAGTATATATATATATAGAGGAGCTACCTTGAGTTTGAATTCAGGATGT
TACAGGAAGAAATATATGTCCAATTCTAATTTATCCAAAAGCAGTTGGGAGAATTACAGG
GATTGGTCCAGACATGTGCTGCGTATGCAAGGTATAGCCCTCATCTGTGGTACTTTGGCAGG
GCTTAGACTGCATCAAAATATTTATAGATGTACATTTGAGTGTACAGTTAGGATCTGATG
TGGAACATTGTAAGATCATTGCTAGAAAACTTTGTCATAATTTTTCAATATTATTCTAA
GTGAATAACCGTAAAGATTTTACATCTTAGCTTCCTTCTTACAGTAAAAAACTATCTG
ATCTCTTGATCAGTATTATAGTAGCCACCTATCACTTTATCTTAACAAATTCTCAATTCC
TTAGGTTTATGTGCTTTTACTTCTTTTATTTGATTAAATTTGCTGTGATGACCTCTCTCT
GCAGAGGGCTGCATCATTGTTGCTATTCTCAAGTGATCTCTTGAGCAATTTAAGAATTG
CCATAAGATTCTAACCTCTGCTGTAACCTATGGTTGTGTGTTCTGGTTAGACCACTAAAT
CTTATTAGCAGTTTAAAAAATTATTCCTTTTGGTTTAGAAGTTAAGACTAAATGCTGAAG
TTTTTGTAACTTTTGGTTTGTATATCATTTCAACTTAAGAAAACATTTGAAGAAAAGGA
CAAAGAATTTCCACTTACCTTTTACCCAGGTTTACCAGTTATTGATAAGTATATCCATTT
GCTTTTACCAGAAAGGCTAACTTGTGTTTAGTTCTCATTTTACCTTTGAGACATTTGGAATA
AATATCAATGTTAACATAAATTGGAATTTTGACTTTGATTTTAGGACCAATGAACAAGCC
AAGTACTTACCTTAGTCATATATAATCCAACCTGTATGGTTATTTGGTATTCAATCCACAC
TTCATTTTACTTGATCTCCCTTAAGATTGCAAGATTGTGTTTGCAGTTTTTCTGAAAATC
TGGGGCTATAAAAGCATCAGGACCTCCCCCGTAGGGGAGGTCGTGTGTTGGGGTCTTAA
CACAAACAGGTTACCTTGAGCTTCAGGAAAAGAACTGGCTCTCAGTTCCCCAGTTCCAGC
TTAATGGGTCTAATTAGGTCTGACCAAAAAGGTGGCAGTTCTTTCCCTCATGTCTCTT
CAGCGCTCCCCGAGACTCTGGAGACTCTGTCTATATCCCTAGGGCTGAGCCTCCCAGGAAC
CATTGGGCTGTTGTGGCATCTGTGTATGCCATGCCAGTGCTGAGGACCTAGTAACAAAC

FIGURE 23.2

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GACAAATGCACAGGCACAGTGGCATTTTTGTGGAACCTCGTATTCCAGCTGTGCGTCTCAG
 AAGAAGCGCACAGCTCCCTCCTGGCTTTCTTAACATAGTGAGCCACTTCCACTTAAGGGT
 CTCCTTACATTCCCTTGAGTTTAATCATTATGAGTTCAGAGGAAAGTCTTTTGATTTTTG
 CTTTTCTTTAAACAGTTCATTTGAGGTGACCTACCCAGTGACTTTGCACCAACCACCAA
 GAAACTTTTTTGCATGCTTCCCGCACCTGTGCCAATCAAGGGAAGGGTTTAAAGGCCTG
 GCGTTTTTTATTCCTCAAAGAAAGGTTTTGCACAGTATTTTAAGGTTCAAGTGCTTCTACT
 TTGTGTTTCAGAAGCAACTGTCTATATACTGTGAAATGACACCTTTTATTTATCCCTTTT
 TATTTATGCAGTATGTCCCTTTTATTTTGGCAGAATTTTTCTAAATGGTGGTTTAAACA
 TTTTCAAGCACATTTTATTGTCCAATATTATAGTAAAGAATGAGAGTTAACAATAACCA
 GTCACATTAAACAAAGATTCCTGTGCGCAGTTGTGAAACCGGTTGTCTTAGGCGTGCCAG
 CTGATGATTGAGACTGTGATCAGGAAAATTTCCACTATTTTCATCAGGCCTAATAGGTAGA
 TTGTGTCTCCAAATGAACTGTGTGGGTTTCCATGCTTAAAGCACAAATAGAGGTGGTGCA
 AGAATCTCCATGAGGGCTTAAATGGCAGTGATGGTTCAGGCGGTAGAGTTTGGAGAAGAA
 GGGATTTGAAACAAACCAAAGGAAAGAAAAGTAAGTAGCCAGAAATCACAAAATGGCATTT
 TTTCTAAAAACAAAGGAAAAGGAATAAAAGAACTAATAAGTTTGAACCCCTACCCCTCC
 CAAATTTGGCAGGGGGGGAGGTATTTTTTTCTATCTATCTAACTAACCCTCTAGAAAA
 CAGTTGACCAAATATAGACTTCTAAATGTTAATCTGCTTTCTCAGTTTCAGTTGAAAAG
 AGACTTTGTTTTGCCTACTGCAGAACTTCTAGGTTCTTTCTTATAGTCTTGGGGTTCTTA
 TTATAGATCGAAAATGTGAGTCGCGCATAATTAAGCCATTTCGGAGTCTTCAGAAGCAGTTC
 ACTCTTGAAATGACTCCGTCGCGCTACAGCCATTTAAGATTTTCAGAACAAAAACAGATCT
 TGATTTTCTTTTCATGTAACTCAAGCTGTTGCTGAGTGGGAGAGTCAGAAATGACACC
 AGCTCCACTGATTACTCAGCTGCTGAAGGATGATTTTTTAAATGCACCTTTACTGTATA
 TGGACTTCCTAATTTCCACCTGTAGAGCATCTTAGGGAGGCTAACATGTCACTCTGGATG
 TTCTTTTAGAATAAGATGCAAATCTATTTTTCTGAAGGCATTAGAGATAGCAAACATTTA
 TTGTGAGTTTACTATATACTAGGCACTGTGCTAAGTGTTTTGCATAGAAAGTTTAAATTT
 CTGGCTTTTTTGTGGCCCAATCATAAGTTTTCATATCAGTTCAACATTCAAATTATATTA
 AGGTACTTAAGAAGAATCCCTGGCTAAATGTGAGGGGCAGTGCCACAGATGGACTGAAAC
 TTTATGCTTATTGCACATTTATGCTATTATTATTGTTGAATTATAGAACCAAGGGAGTG
 TGGAAGCCACTGGAAAAATATGAGACTTAGATACATAATTTGAGTAAAAATGGCTCAAA
 GTCATGAGGGTAAAGTTTTTTGTATTTCCATTTTATTCGAGCGGCATCGTTTTTAAAT
 CATTATGAATTTGACCCTATATAGATGTTTCCAAATAATTCTTTTTCACCTTCATAAAAT
 TCCTTCCTGTGGCTGTGAGATGCCTTGCCTATCAGTTTCAAGCTTAGTTGTCTTTCTCA
 TCCTTTACCATTTTAGCTTTAAAAAACAAAGTGACAATTAGAACTTCCTGCCTGTGCGG
 CCTCACTGAAAGACCGATATTGGCCTGATAAGGAGATATTTATTTTGTTTTAGTGGCTTC
 AGAAATCCCTCTCCCTCAGCAAGCTTTCCATCACGGCCCCCGTCAGCATCTTCCCTGA
 TAGCGTTCTTCTGTGTTTATTTCTGGGGCTTCAGGCTCGCCCAGGAGGAAGTGAATACC
 GCTGGCAGGAGATAACATTCTCTAAGGGGCTCTCAATTTGGAATCGAATCCCTCAAGCCA
 GTCAGCCTAGAGAATAACATTTAAAGGGTTTCAGTTCTGGAGTTTTCACAGAGTTTCATTTCTA
 GACCTATCAGATAGCAAGTGTGGAGTTCTTTCTCACTAAATTCAGCAGAGACATTTTTT
 TAGACGATGAAGGATATTTGCACAAAGGCTTCAGCATGATCCCCCAACCTGCTGCCTCT
 GAAGGCATCTCCACACATTGACAGCCAATGCCTTCAGTGCGTTCTTAGGGCAGGTGTCCT
 GGCTTGAGTGACTGTCTCCAATAATCAGAGCTCAAATAAACATCGTATGTTTTACTTT
 TGGTTTCCAGGCAAGGCTGAGCAGGGAATTTTCAGTTTCCCTGCCCAGATGGGTGTTTT
 TTCCTGAAGGCATCATTTATTGTGTAGCGAGGAGACAGGGCTGGCTGTGCGAGGGATAGT
 CTAGAACTGTCTCATTGCTGCTGTTCTTAAATAGTATCTTTACCAAGTAATAACGTGCC
 GTCTTTGGGAATAAGTGCTTTCTCTTAGCCTGTTCTGTTTTCTTGGGTGCGCTAAGTAA
 TTGAAGTGGCTCAGGAAGTACCTATTGTGGTTTGGCAGAGGTGACTGTCACGCCCTGTGA
 CTCCAGGGGCCAGCACTGCTGGGATCCTGGCTAGACCAGACAGAGCCTTGGTGAAGTGCT
 TAGGCTGTCTGCACATCGCGAGGAAGGTGGTATTCACTTCGCTAAGCTCCTTGGCATAGG
 CAGTTTGAACAGGGCTTTATCAAATTCGTATTCAACAAGAGTAGAAGCGAAAATTGATGA
 CTGTGTATTACTTGAAATGAGTCTTAATCTTTACATTTAGTTCTCAGGGTATGCTGATT
 TCCTTTAGGTAAACCATGAACATCAGAAAGACTTTTATTAACCTATGACAGGGTCCCCAC

FIGURE 23.3

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CCCAGTATTTTCCACTCCATTAAATGGAAGTTTTTTTTTTTTTTCTTTTTTGAGAC
AGAGTTTTTGCTCTTGTTGCCAGTCTGGAGTGCAATGGCACAATCTCGGCTCACCACAAC
CTCCACCTCCCAGATTCAAGCGATTCTTCTGCCTCAGCCTCCCAAGTAGCTGGGATTACA
GGTGTGCGCCACCACGCCCAGCTAATTTTGTATTTTAGTAGAGATGGGGTTTCTCCATG
TTGGTCAGGCTGGTCTCGAACTTCCGACCTCAGGTGATCCGCCCACCTCGGCCTCCCAA
GTGCTGGGATTACAGGCAAGAGCCACTGCATCCAGCTTAGGCTATCTTACTCCAGCCTAA
ACAGCAATTTTCTATCATAAGGTCTGTACTAATGAAAACAGAATCACCCAAGGCTGCTGT
TTGTTCTGTCTGTGCTGCCATTGTCCGCATTTTGTCTGAGGAGGAAACGGAAGTGCATTT
TGAGTGAGTGGCCAGAGCCTTCTAGAATGAGAGTGCGTTGGAAGCCAGATATGTGGCGA
TTGTGTGCGCCAGCTGTTACTCAGGTTTTCTCAAGAAGGAGGAGCAACTTTGGCAGTTTTG
CTTCAGTTCTCTCTAGCCCTCTGTGTAAATCGCCCTTTTTCTTTATTTTTCAGCACAAACAC
AGAGCAGTCTAAAGCAACCGAGCACTGAGAAAAATGAACTCTGCCCAAAGAATGTCCCAA
AGAGAGAGTACAGCGTGAAAGAAATCCTAAAATTGGACTCCAACCCCTCCAAAGGAAAGG
ACCTCTACCGTTCTAACATTTTCAACCCCTCACATCAGAAAAGGACCTCGATGACTTTAGAA
GACGTGGGAGCCCCGAAATGCCCTTCTACCCCTCGGGTCGTTTACCCCATCCGGGCCCTC
TGCCAGAAGACTTTTTGAAAGCTTCCCTGGCCTACGGGATCGAGAGACCCACGTACATCA
CTCGCTCCCCCATTCATCTCCACCACTCCAAGCCCTCTGCAAGAAGCAGCCCCGACC
AAAGCCTCAAGAGCTCCAGCCCTCACAGCAGCCCTGGGAATACGGTGTCCCCTGTGGGCC
CCGGCTCTCAAGAGCACCGGACTCTACGCTTACTTGAACGCTCTACGGCAGCGAAG
GTTTGGGCTCTACCTGGCTACGCACCCCTGCCCCACCTCCCGCCAGCTTTTCATCCCT
CGTACAACGCTCACTACCCCAAGTTTCTCTTGGCCCCCTACGGCATGAATTGTAATGGCC
TGAGCGCTGTGAGCAGCATGAATGGCATCAACAACCTTTGGCCTCTTCCCGAGGCTGTGCC
CTGTCTACAGCAATCTCCTCGGTGGGGGAGCCTGCCCCACCCCATGCTCAACCCCACTT
CTCTCCCGAGCTCGCTGCCCTCAGATGGAGCCCGAGGTTGCTCCAGCCGGAGCATCCCA
GGGAGGTGCTTGTCCCGGCGCCCCACAGTGCCTTCTCCTTTACCGGGCCGCGCCAGCA
TGAAGGACAAGGCCTGTAGCCCCACAAGCGGTCTCCACGGCGGGAACAGCCGCCACGG
CAGAACATGTGGTGCAGCCCCAAGCTACCTCAGCAGCGATGGCAGCCCCAGCAGCGACG
AAGCCATGAATCTCATTAAAAACAAAAGAAACATGACCGGTACAAGACCCCTTCCCTACC
CGCTGAAGAAGCAGAACGGGAGATCAAGTACGAATGCAACGTTTGGCGCCAAGACTTTTCG
GCCAGCTCTCCAATCTGAAGTAGGCTTGAGAGAGAGCAGTCCAAGGGGCTGTGAGTGC
ATGCTTGTGTTTGTATTTAGCTTGCTTTCCATGGGGTATCGATTGCATTTGCAGTAGTAT
GAGCCCCCGTTTGGGGATAGTGGGTATGGATTCCGCCTGGCTTTTGCCACTTCTAGCTCT
TTGACTTTGGACAAGTGACTTCCCTTCTCTGATTTTCTTCTGAATAATAAAAAAATTAG
GGGTTTGGACTAGAAGATTAGGTGAACTCCCTGCTAGCCTGTGATTTTTGTGCTTTAA
GAAAAACACCATTCTGAAAACATGAAGATTTCTTCTTTTAAGACTGTCTTGATGCTTTT
CTTAAGATATTTGCATCAACACTTGAGTCTTGAGCAGAAATGTTAGGTCTCAGAGCCAG
CTTGAGAGCAGAGCTAACACATGTGGCTTCTTCCAGGTCCACCTGAGAGTGCACAGTGG
AGAACGGCCTTCAAATGTGAGACTTGCAACAAGGGCTTTACTCAGCTCGCCACCTGCA
GAAACACTACCTGGTACACACGGGAGAAAAGCCACATGAATGCCAGGTGCGCAGTATTTT
CTGGGTAGACCTTCTGACCTTTGTAGAAAATGTCTGTGAGTACCCTCCCATGTCCTATA
TAGCCCGTAGTTAAAGCCAACACCAGATTCTGCGTTGTCCCATCCTGGACTGATGGCACT
ATGGTCCTTCCCAGTACTTTGTATCTGCTGATGACTTGAGATGGCACAGCCAGCTTCCAG
TGGGTGGGAAAATGGTAGGGGAAATAAACAGCCCTCGTGTGCTGTGTGCCACATCCCC
CCGTTTGTCTTAATACCACACTGGAGGTGCCACAAGGAGGCTTCTCACCTCCTAGGTTGCT
GGGCGTTGGCCGGTAAGCCTGCCCCCTCCGTTGGCAACTCTTAATCTTCTGGCCTTCCTG
TCTCCCTTCCCTGCTGTCTCTCTCCCTACACTGTAGGCTCTGCCACAAGAGATTTAGCAG
CACCAGCAATCTCAAGACCCACCTGCGACTCCATTCTGGAGAGAAACCATACCAATGCAA
GGTGTGCCCTGCCAAGTTCACCCAGTTTGTGCACCTGAAACTGCACAAGCGTCTGCACAC
CCGGGAGCGCCCCACAAGTGCTCCAGTGCCACAAGAACTACATCCATCTCTGTAGCCT
CAAGGTTACCTGAAAGGGAAGTGCCTGCGGCCCGGCGCCTGGGCTGCCCTTGAAGA
TCTGACCCGAATCAATGAAGAAATCGAGAAGTTTGACATCAGTGACAATGCTGACCGGCT
CGAGGACGTGGAGGATGACATCAGTGTGATCTCTGTAGTGGAGAAGGAAATTCTGGCCGT

FIGURE 23.4

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GGTCAGAAAAGAGAAAAGAAGAACTGGCCTGAAAGTGTCTTTGCAAAGAAACATGGGGAA
TGGACTCCTCTCCTCAGGGTGCAGCCTTTATGAGTCATCAGATCTACCCCTCATGAAGTT
GCCTCCCAGCAACCCACTACCTCTGGTACCTGTAAAGGTCAAACAAGAAACAGTTGAACC
AATGGATCCTTAAGATTTTCAGAAAACACTTATTTTGTCTTAAAGTTATGACTTGGTGA
GTCAGGGTGCCTGTAGGAAGTGGCTTGTACATAATCCCAGCTCTGCAAAGCTCTCTCGAC
AGCAATATGGTTTCCCCTCACCTTGAATTAAGAAGGAACTCCAAAGTTACTGAAATCT
CAGGGCATGAACAAGGCAAAGGCCATATATATATATATATATATCTGTATACATATTA
TATATACTTATTTACACCTGTGTCTATATATTTGCCCTGTGTATTTTGAATATTTGTGT
GGACATGTTTGCATAGCCTTCCCATTACTAAGACTATTACCTAGTCATAATTATTTTTTC
AATGATAATCCTTCATAATTTATTATACAATTTATCATTCAGAAAGCAATAATTAACAAA
GTTTACAATGACTGGAAAGATTCCTTGTAATTTGAGTATAAATGTATTTTGTCTTGTGG
CCATTCTTTGTAGATAATTTCTGCACATCTGTATAAGTACCTAAGATTTAGTTAAACAAA
TATATGACTTCAGTCAACCTCTCTCTAATAATGGTTTGGAAATGAGGTTGGGTAATT
GCCAATGTTGGACAGTTGATGTGTTCATTCTGGGATCCTATCATTTGAACAGCATTGTA
CATAACTTGGGGGTATGTGTGCAGGATTACCCAAGAATAACTTAAGTAGAAGAAACAAGA
AAGGGAATCTTGTATATTTTTTGTGTAGTTCATGTTTTTCCCCAGCCACAATTTTACC
GGAAGGGTGACAGGAAGGCTTTACCAACCTGTCTCTCCCTCCAAAAGAGCAGAATCCTCC
CACCGCCCTGCCCTCCCCACCGAGTCTCTGTGGCCATTGAGAGCGGCCACATGACTTTTGC
ATCCATTGTATTATCAGAAAATGTGAAGAAGAAAAAATGCCATGTTTTAAACCACTGC
GAAAATTTCCCCAAAGCATAGGTGGCTTTGTGTGTGTGCGATTGGGGGCTTGAGTCTGG
GTGGTGTTTTGTGTGTGGTTTTTGTGCTTTTTTTTTTTTTTTTTTAAATGTCAAAAT
TGCACAAACATGGTGCTCTACCAGGAAGGATTGAGGTAGATAGGCTCAGGCCACACTTT
AAAAACAAACACACAAACAACAAAAACGGGTATTCTAGTCATCTTGGGGTAAAAGCGGG
TAATGAACATTCTATCCCCAACACATCAATTGTATTTTTCTGTAAACTCAGATTTTC
CTCAGTATTTGTGTTTTTACATTTTATGGTTAATTTAATGGAAGATGAAAGGGCATTGCA
AAGTTGTTCAACAACAGTTACCTCATTGAGTGTGTCCAGTAGTGCAGGAAATGATGTCTT
ATCTAATGATTTGCTTCTCTAGAGGAGAAACCGAGTAAATGTGCTCCAGCAAGATAGACT
TTGTGTTATTCTATCTTTTATTCTGCTAAGCCCCAAAGATTACATGTTGGTGTCAAAGTG
TAGCAAAAAATGATGTATATTTATAAATCTATTTATACCACTATATCATATGTATATATA
TTTATAACCACTTAAATTGTGAGCCAAGCCATGTAAAAGATCTACTTTTTCTAAGGGCAA
AAAAAAAAAAAAAAAAAAGAACACTCCTTCTGAGACTTTGCTTAATACTTGGTGACC
TCACAATCACGTCGGTATGATTGGGCACCCTTGCCCTACTGTAAGAGACCCTAAACCTTG
GTGCAGTGGTGGGGACCACAAAACAACCAGGGAGGAAGAGATACATCATTTTTTAGTATT
AAGGACCATCTAAGACAGCTCTATTTTTTTTTTGCCACTTTATGATTATGTGGTCACACC
CAAGTCACAGAAATAAAAACTGACTTTACCGCTGCAATTTTTCTGTTTTCTCCTTACT
AAATACTGATACATTACTCCAATCTATTTTATAATTATTTGACATTTTGTTCACATCA
ACTAATGTTTACCTGTAGAAGAGAACAAATTTTGAATAATCCAGGGAAACCCAGAGCCT
TACTGGTCTTCTGTAACCTCCAAGACTGACAGCTTTTTATGTATCAGTGTGTGATAACA
CAGTCCCTTAAGTGAAGGTAAACCAAGCATCACGTTGACATTAGACCAAATACTTTTGAT
TCCCAACTACTCGTTTGTCTTTTTCTCCTTTGTGCTTTCCCATAGTGAGAATTTTTAT
AAAGACTTCTTGCTTCTCTCACCATCCATCCTTCTCTTTCTGCCTCTTACATGTGAATG
TTGAGCCCAATCAACAGTGGTTTTATTTTTCTCTACTCAAAGTTAAACTGACCAA

FIGURE 23.5

09719534-011801

[illegible]

FIGURE 24

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GAATTCGGGAAGCCAGACGGTTAAACACAGACAAAGTGCTGCCGTGACACTCGGCCCTCCAGTGTGCGG
AGAGGCAAGAGCAGCGACCGCGCACCTGTCCGCCCGGAGCTGGGACGCGCGCCCGGGCGGCCGACGAAG
CGAGGAGGGACCGCCGAGGCTGCCCCAAGTGTAACCTCAGCACTGTGAGGTTTCAGGGATTGGCAGAGG
GGACCAAGGGGACATGAAAATGGACATGGAGGATGCGGATATGACTCTGTGGACAGAGGCTGAGTTTGAA
GAGAAGTGATACATACATTGTGAACGACCACCCCTGGGATTCTGGTGCTGATGGCGGTACTTCGGTTTCAGG
CGGAGGCATCCTTACCAAGGAATCTGCTTTTCAAGTATGCCACCAACAGTGAAGAGGTTATTGGAGTGAT
GAGTAAAGAATACATACCAAGGGCACACGTTTTGGACCCCTAATAGGTGAAATCTACACCAATGACACA
GTTTCCTAAGAACGCCAACAGGAAATATTTTTGGAGGATCTATTCCAGAGGGGAGCTTCACCACCTTCATTG
ACGGCTTTAATGAAGAGAAAAGCAACTGGATGCGCTATGTGAATCCAGCACACTCTCCCGGGAGCAAAA
CCTGGCTGCGTGTGAGAACGGGATGAACATCTACTTCTACACCATTAGCCCATCCCTGCCAACCAGGAA
CTTCTTGTGTGGTATTGTGCGGACTTTGCAGAAAGGCTTCACTACCCTTATCCCGGAGAGCTGACAATGA
TGAATCTCACACAAACACAGAGCAGTCTAAAGCAACCGAGCACTGAGAAAAATGAACTCTGCCCAAAGAA
TGTCCCAAAGAGAGAGTACAGCGTGAAAGAAATCCTAAAAATGGACTCCAACCCCTCCAAAGGAAAGGAC
CTCTACCGTTCTAACATTTACCCCTCACATCAGAAAAGGACCTCGATGACTTTAGAAGACGTGGGAGCC
CCGAAATGCCCTTCTACCCCTCGGGTCGTTTACCCCATCCGGGCCCCCTCTGCCAGAAGACTTTTTGAAAGC
TTCCCTGGCCTACGGGATCGAGAGACCCACGTACATCACTCGCTCCCCATTCCATCCTCCACCACTCCA
AGCCCTCTGCAAGAAGCAGCCCCGACCAAGCCTCAAGAGCTCCAGCCCTCACAGCAGCCCTGGGAATA
CGGTGTCCCTGTGGGCCCCGGCTCTCAAGAGCACCGGACTCCTACGCTTACTTGAACGCGTCTTACGG
CACGGAAGGTTTGGGCTCCTACCCCTGGCTACGCACCCCTGCCCCACCTCCCGCCAGCTTTCATCCCTCG
TACAACGCTCACTACCCCAAGTTCTCTTGCCCCCTACGGCATGAATTGTAATGGCCTGAGCGCTGTGA
GCAGCATGAATGGCATCAACAACCTTTGGCCTCTTCCCGAGGCTGTGCCCTGTCTACAGCAATCTCCTCGG
TGGGGGCAGCCTGCCCCACCCATGCTCAACCCCACTTCTCTCCCGAGCTCGCTGCCCTCAGATGGAGCC
CGGAGGTTGCTCCAGCCGGAGCATCCAGGGAGGTGCTTGTCCCGGCGCCCCACAGTGCCTTCTCCTTTA
CCGGGGCCGCGCCAGCATGAAGGACAAGGCCTGTAGCCCCACAAGCGGTCTCCACGGCGGGAACAGC
CGCACGGCAGAACATGTGGTGCAGCCCAAAGCTACCTCAGCAGCGATGGCAGCCCCAGCAGCGACGAA
GCCATGAATCTCATTAAAAACAAAAGAAACATGACCGGCTACAAGACCCTTCCCTACCCGCTGAAGAAGC
AGAACGGCAAGATCAAGTACGAATGCAACGTTTGCGCCAAGACTTTTCGGCCAGCTCTCCAATCTGAAGGT
CCACCTGAGAGTGACAGTGGAGAACGGCCTTTCAAATGTGAGACTTGCAACAAGGGCTTTACTCAGCTC
CCCCACCTGCAGAAACACTACCTGGTACACACGGGAGAAAAAGCCACATGAATGCCAGGTCTGCCACAAGA
GATTTAGCAGCACCAGCAATCTCAAGACCCACCTGCGACTCCATTCTGGAGAGAAACCATACCAATGCAA
GGTGTGCCCTGCCAAGTTACCCAGTTTGTGCACCTGAAACTGCACAAGCGTCTGCACACCCGGGAGCGG
CCCCACAAGTGCTCCAGTGCCACAAGAACTACATCCATCTCTGTAGCCTCAAGGTTCACTGAAAGGGA
ACTGCGCTGCGGCCCCGGCGCCTGGGCTGCCCTTGAAGATCTGACCCGAATCAATGAAGAAATCGAGAA
GTTTGACATCAGTGACAATGCTGACCGGCTCGAGGACGTGGAGGATGACATCAGTGTGATCTCTGTAGTG
GAGAAGGAAATCTGGCCGTGGTCAGAAAAGAGAAAGAAGAACTGGCCTGAAAGTGTCTTTGCAAAGAA
ACATGGGGAATGGACTCCTCTCCTCAGGGTGACGCTTTATGAGTCATCAGATCTACCCCTCATGAAGTT
GCCTCCAGCAACCCACTACCTCTGGTACCTGTAAAGGTCAAACAAGAAACAGTTGAACCAATGGATCCT
TAAGATTTTCAGAAAACACTTATT

FIGURE 25

[illegible]

FIGURE 26.1

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GCTACTGCCACCGCCACGGCCACCACCACAACCTACTACCCTACCATTTCACCACATCACCTCTACCATCA
CTACTGGCCTCATGGATAGCAGTCACCTGGAGATGACGTCCTGGGCGGCTCTGCCCCCTTCTATCCAGCAG
CAGCACTAATGTCCGGAGACCCAAGCTCACTTTTGATGACTCGGTTTACAATGCTGATTATTACATGCAA
GAAGCTAAGAAGCTGAAGCACAAAGCTGATGCACTGTTTCGAGAAATTTGGCAAAGCTGTGAATTATGCTG
ATGCCGCCCTCTCCTTCACTGAATGTGGCAATGCCATGGAACGCGACCCTCTGGAAGCAAAGTCCCCATA
CACCATGTACTCTGAGACTGTGGAGCTCCTCAGGTATGCAATGAGGCTGAAGAACTTTGCAAGTCCCTTG
GCTTCGGATGGGGACAAAAGCTAGCAGTACTATGCTACCGATGTTTATCACTCCTCTATTGAGAATGT
TTAAGCTGAAGAAGGACCATGCTATGAAGTACTCCAGATCACTGATGGAATATTTTAAGCAAATGCTTC
AAAAGTCGCACAGATACCCTCTCCATGGGTAAAGCAATGGAAGAACAACCTCCATCCCCAGTGTCTCTCAAC
AACGCTCCCCCATCAACGCAATGGGGAACCTGAACAATGGCCAGTCACCATTCCCCAGCGCATTCACC
ACATGGCTGCCAGCCACGTCAACATCACTAGCAATGTGTTACGGGGCTATGAACACTGGGATATGGCCGA
CAAACCTGACAAGAGAAAACAAAGAATTCTTTGGTGATCTGGACACGCTGATGGGGCCTCTGACCAGCAC
AGCAGCATGACCAATCTTGTCCGCTACGTTCCGCAAGGACTGTGTTGGCTGCGCATCGATGCCCATTTGT
TGTAAGTGGGTGTTCTCAGATCTCTAGCATCAGGACCCATCACTCTACCTCTACCAGCGCACTGATGGTCA
CTGGTGAACTCCACTCACTGGGGAACGTTCTCTTTGGTTATGTTTGTGTTTTATGCTTCTTTTGTATCT
GTAAAAACAGAAGTCATTGTAAGTTGACACTACAACCTTAAGGGCAGTGACGTTTTATTACTTAGTCAT
TTTTTTCTTTTAGCATTTGATATGCATTTCTCAGATTCCACCATCTTTTGTGCTTTATGGAATGACAG
TCCCTACAATATTGTTTTAAGCCACACTACCCAAAACAAAGAATGGGAAGCACTTGTGATAAAGACAGG
CTCCTGAGAAATGCAACAAGTGGTCTTACATATACATGAGAACTTAGACACAAGGGACCATCCCCAAAC
TCTACTCTTATACCCAGAAAAGAACATATTTAGAATCTGTCAAACCTTTTGTGTATCCACAGATTCAAT
CTTCAGGTGAGAATTTTCAATGTCAAACCCACTGGTTAGATGTTGTAGCAACATCATAAATCAAGAGT
ATCAAGAAAATAAATGAGCATAGCAATGCTACTCTTAAAAAGATGCTATGCCACACAACCAGAGGACTTT
CTTGTTAGCATCCCTTTCTGATTCCTTATTTTGTAAATTTAATGATAAGAAGAAAGGGTGACATTTAT
TTTGACAAGTTTTAGGCATCAGCTGGCATCAGTGTGTTTCAACTCCATTATTTGAAGTGTAATCCTCAC
CTGGGGTCTCTGTGTGCAAAGCTGTCCTTTTGAAGAACAGTTTGGTTGATGCATGCCCTTAGTAGCCAAA
ATGCTACACTCTAGACTTACAAGTGGGAGTTAAGAGAGGTCTGGAAAGTGCCAACAAGGAATTCACACC
TCTGCCCTCCTTTGCAACAACAACATTTACACAGTTGGTAAGTGGGTCCATAACTGSCAGGATTTTTAAAT
TGTAATTTTGCTCAAATCTATGGGAACAAAAGTCAAGGTATCACTACCTAGAAGTAATGATATACAGTTTT
CTTCCTAGTGGCTTGAAAATCTGGACTTCCTCAATTATTATTACATTTTCTCTTATAGGTTTCTGT
TTTCTACTTTCTTTTTCTCTTATCTGTGTTTCCCTTTCTTTGTTGGCTCATTAACCTTTTGACTGAAT
TACAATTACTCCTTTTATTAAAGTCCATATTATTGTGAATCATTTCATGAAAATTTCTAAGAAAACCTCC
AAACTCTCTAAATAGTAGCTAATTTTATTTTTTAAATGAGTCGTGGGGTAGTGCTTCACCTTGAGAT
GCTTTGAAAGAGCCCTAAACATTGGGAACCATTCACCTAATTTGGAGACATTTCTCACTGGTTGTGACTA
CCCCCTTATGATCCTTCACATTCATTTTATGTCCCTAAACATCACAATGTAAATATCATTTTTGATGTTT
CAGCTCACCAGAAGATTCTTACACTTGGGGTAAACACTATCCATGCATTACTTACTGGTAATTACCTGCT
GGTATATAATTCCATGTAGCCTTTAATATGCTGGGTATCAAATCTGTTCACTGAGTTATGACCAGATA
AATAATAGATATGCACATGAAAGATGCAAACTTGTGTGATTATTAAAGCCAGCCATGCAGGTCCATGATA
GAAACAGCAGGTGATGACTCTGCACTCTCATGTGCAAGGTAGCTATATCCCCAGTTGCAAAACAGCCAG
ACTTGAGCTGTGCTCTGGTCACTTTTGAAGTCTTAAAGGCCTTTTGTGTGATAAGGCTGTGGAAGTTGTACTC
CAATGGCTGAAGCCATGTTGTTAATATGGCTGATGGGAGCATCCCTGCAGCTGAACCCAGCACTTTTTAT
GCTCCCACTGTGGTTGAGCTTTATGTTTACAGTCTCAGCAACAACACTTATGCATCCAAACACTCACAAA
TGAAACCTGAAAGAATCTTTCTGAGCCTCTTAAAGAGGAAAATGATGATAACATTAAAGACTCTGAAC
ACCCAAGGTGGTGTACATATAAAAAATTAAGCTGATGACTTTGCAGTGACTCAAGTTGTCTCTTTATCA
TGGTTTACCAGGTAGAGTGCCCTGGCTATTACTATATAATGAAGCCCACTGGCTTGACTTGTAAGTTCAAC
CTAAACCACAATCCTAGACCATCATGGATTAGGAGTAGATTCTTCTTGAAATCCCACATCCAGAACTA
GACATTAGAATGTTGAGGCAGTTTCCAGAGAAAACAAGCATATTGCCTCATGGATGAAAGACTTGTAAGTT
CTAGTTTCACTGACTTGTTATATCTACTATACACAACAGGGAGGCAAGAGGATTCTCTGTCTCTCTGG
TGACTGAGTGTAATAATATGTGCCAAGTCTGCAGCAGTGACCAATCTGACAATCGAGCTCTGGATCAC
CACTTGATTATGTAGTAGACTCATTTTATAAAGCAGCTTAGGAACCTAATTAAACATGGAGGATGAATTACC
TTCCTATCCCTTGAGATAAGACATCTTTCACTTTTATGATTAAAGGATTGTTGCTGTTTTATAGTTACTCT
GTTTCATCAGTGTAATGGTGATGCGTGTGCTAGGTGTGAGCTATTTGAGGGACTAAGGGATGGAGAT
ATTCTGTCAAATGAATCTCTTCACTATACCACTTTGTGGGAGGATATGAGACATGTGGATGGCAGTGAG

FIGURE 26.2

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AGATCGTGCCTCTAGATCTTGATGGAGGCTTGGTGAGACACACTTAAATAAGCACGTGGAGGTTAGAATA
GAGGGCAGAGTAAAAGGAAGCTCCATCTGAGCAAGTACACCAAATGATCTCAGCCCTGCAACTTGACCCA
GGTAGGGCCACCCTACGCCTTCACTTGTCAACCAAGCTCCAACCACAGAGAGTTTGACAAGTTTGTGTT
ATGATGTTGGCTTGGCTTTGTATTTTAACTTGGATTTTGTAGTGGTTTGTGCATATAACTGTCTG
AGTTTGGTAGGTAGGATTACTTTGAAAAGGGTTTACTAGTGTGGTCTCCGGGTAGAATTTAGCTGTAAC
ATGTTGTTAGCCAGCTGTAGACTGTTAATTACTTAATAATCTCATTGGGAAAATACTAGTAGTTTATA
TTTGGATGACATAATTGGAAAAAGCAGATTAGCTCTACTACTTTTAAAAGACTTAAGGTCGGGATGCCT
TTTTTTCCATGTAAGGAAATGAAAAGACCCAAAATCTTCAGGCAAAAAGCAAGTTGCAAAATTAGAAACC
ATTGGCTAAAAATGTGTTTTTGTGAGTTTCCAATGGATGAATTTTCATTTGGACATTACATCACTAAAT
TCATTAGATTTTGTCTGCATTGGAAAAGATACTCTTCTAGCATATCTTTCCCAAAGATATCTAATTTGGAT
TCTGTTTTCATGCAATTTGCATCCCGGAGGTTGAAGTTGGAGTTTGGAGTTGGAAAATATCTTTGAAGGC
AGAATCAGTTGAGTTGTGAGGGTGAAGCCTCACATACTTCTCAACAGACATGATAAAATTCACCTGCATG
AGTTGGCAGGTGGGAGAACCAACTGGATCACTGGGTAAGACTACTCAGTAAAGCAATGAAGTCTTGCT
TAGAGAAGCATCACTATCCCATTTGAGAAAAATGTGTGGCAAGATGATACAGCTACACAGTATCAAATGA
ATGGGTCAATTGAGCAGCTTAAATTTCTGTGGGGAAAAATTTAGAGCCAGTTGTGAGTGTCTG
TTACATGACTGGCAGACTAAATTTCTCATCGTTGTTGTTATTGTTGTTGTTGTTTCTCATTTTCACTCGC
ACGGCCTTATTCTCATAATTAATAATCTAATTCATTTTCTCTTTAGTGTAGTAGACTCCAACAACAGAAG
TGGCATCTGTGATTTCATAATCAGCATTACCTGGCAGGAGACTAATCAGATAGGCCGGTCTCAGACAT
TAATCCTACCATCTGATATTTTGGTGAAGGAAAAAGTATTAATTTCTCTTTCCATCCTCCTCAGAAA
TATAGAAGCCCTCTTTACCAAATCATCACATTTTACTCTGTAATCTACCAGCTAAAAGAAAAATTGCATT
GAAGCCCCACAAAGCCAGATTGCAGTTCTTGCCCCCTTTTGGCTCTGACATGAGATGTTAAAGAATTATT
CATTGTGCTCACATTGGGTTAGGGGACACTGAAGTCTTTTAGATCCATGATCAGTCATCATTCTCTA
AGAGATTGGAGCTTTGCTGTTTCATTAAGTGTGAGTGTAGACTAATGGTGTAAATAAAAAATCATTCAA
AATTTCAAATCTTTTGCAGTGACCTCAATTTTGTGGCTCTGTGATTTGTATCAGACTTTGAGGAGGG
AAGGGGGAAGTGAAGGAAGCCTACGTCCAGGCCCTGACAGGATGCTGCAGTAGCAAGCTCAAGCTCGCC
TGCTGCCAGCAGTTGCTGGTGAGCAGCATGACAGCAGCTGTGGGAAGCCTCCTGAAGAATGCCCC
AGCTGATGCTTTGAGCTGGGAATAGTTTGTTCCTATTGGGGAAGTCAATGTTCTCAGTCTCTGCAGCAG
GAAGCCAGCTGTGATATTCGGAGGGAATTTGAGATGCTTTTACCTTTTGGTTTTGCTGCTGCTCACTCAT
GTGGCTACGAAAGTGTCTCTGAGAATAGAGCCCAATGTGGTGACAATGGGTAGTCAAATGCACCCAGAT
GCTCAAGCCCTGTTGTGGTTCTGCAGTGTATGAAATTTGGGAGGAAGGAGACCCTGGACAGTAAGCAAA
ATTGGAGACACTCCAACGAGGCTAAGTTAATGCCGTGTTGCCCAGAACAGATCTAGCTTCTCATTTGGT
CAGCCTAGCATGCAACCAGTGGTGTGCTGGTAAATGTTTAAACACAGCTCGCTGAGAATAGAAAGCAC
CTGGTTTGCACCATTTGCCAATTTCCATGGCATAAATACTACCACTTTAGATGATTTTAAAGCTACCACT
GTGATGTCACTGAACACATGGTTGGAAGAGATGCACGCAGTTGGCTCTTGCAAGCCTGGGCAAAAATGC
TTCAACACGCCACTGGATGCAGCCAGTCAGAGGGTTCATATTTAATATATGTGTTTCATGTGGACACACAC
AGACACACACACACAACTACCCCTTACACACACACTTCGATGACTAAAACAATTACATAGTTTAAAGAT
ATGAATCAATGTGTGAATGTAGAAAGCTTATGATAAGGCCCTAGAGGTATGGGTTGCCCTGGAAGCCTAG
GTTTTAAGCAGGAGAAATAGCTGAGAAGAATGAAGCCCTCCTGAGCTGAAAGGAGAGATGGATCAATGGAG
ATGGTTCCATCATCTCCTTCCATATCTCACAGGTAATAATGGGCACTCAGAAAACCTCAGCATGATTTT
TTAAAAAGATAAGTGAGTGTTTTTTATTTTATTATTATGTCATCATTATTTTGATTTACAAATGCTATT
TGTAACTTTTTACATGTAAGTAAAGTATTTACGGGAAGTCTATGGAGAATAGCACAAATCCAGAATT
TACTGTGTTTTTCTTTTATGTGACGTGGAACTCAGTAATTTCTCCACCTTACATTGTTGTTTCATAAGA
ATTTTACTTTTAGTTATTAGGGAATCTAAGTTTTTGTAAACATTTGTTTTTAGTTAAAGTATCTACTTA
CTGTTTTAGCTCTGAATCAAACAGAAATATCTCTGTATCAATTGCATGACTATTGAGAAACAATAATCC
AAACCAAAATAATTTCTTTTCCACCCAGTACGAAGAACTAAGCTCAGTAACAAGAAGGCATAAACTAA
AGTATATAATGAGGCTTTTCAATTAATACACACACACACACTCACACACACACATACACTTTTTAA
TTTTTAAATTAGGCCTCCACACATAAATCATTTTGAAGTAGAATAGAAAATCTCAAAGAATTCATTCTC
CTGGTCTGTGCATCTTCTGCAGTTAATAAGAGGTTTGTATCTGGAAAGATGGAAGAAGTCTGTTCTAAAA
TCTTATTTTTTCAAAAAAAATTTCCATTTTCTCTCTGGGCTGTATCCATGGTTGAATGTTAGCCCTGGA
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FIGURE 26.3

FIGURE 26.4

Declaration and Power of Attorney for Patent Application
Déclaration et Pouvoirs pour Demande de Brevet
French Language Declaration

En tant l'inventeur nommé ci-après, je déclare par le présent acte que :

As a below named inventor, I hereby declare that :

Mon domicile, mon adresse postale et ma nationalité sont ceux figurant ci-dessous à côté de mon nom.

My residence, post office address and citizenship are as stated next to my name.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers co-inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed an for which a patent is sought on the invention entitled

Nucleic sequence and deduced protein sequence family with human endogenous retroviral motifs, and their uses

et dont la description est fournie ci-joint à moins

the specification of which :

☐ ci-joint

☐ is attached hereto.

☐ a été déposée le

☒ was filed on

sous le numéro de demande des Etats-Unis ou le numéro de demande international PCT

as United States Application Number or PCT International Application Number.
PCT/FR99/01513 filed on June 23, 1999

et modifiée le

and was amended on

(le cas échéant).

(if applicable).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait références ci-dessus.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

Prior Foreign application(s)
Demande(s) de brevet antérieure(s) dans un autre pays.

(Number) (Country)
(Numéro) (Pays)

98 07920 FRANCE

(Number) (Country)
(Numéro) (Pays)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365(c) du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande :

(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

Je déclare que par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique ; et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la section 1001 du Titre 18 du Code des Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Priority claimed
Droit de priorité
revendiqué

(Day/Month/Year Filed) ☒ ☐
(Jour/Mois/Anné de dépôt) Yes No
Oui Non

23.06.1998

(Day/Month/Year Filed) ☐ ☐
(Jour/Mois/Anné de dépôt) Yes No
Oui Non

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (Filing Date)
(N° de demande) (Date de dépôt)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Status) (patented, pending, abandoned)
(Statut) (breveté, en cours d'examen, abandonné)

(Status) (patented, pending, abandoned)
(Statut) (breveté, en cours d'examen, abandonné)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

French Language Declaration

POUVOIRS : En tant que l'inventeur cité, je désigne par la présente l'(les) avocat(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marques : (mentionner le nom et le numéro d'enregistrement).

POWER OF ATTORNEY : As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to persecute this application and transact all business in the Patent and Trademark Office connected therewith : (list name and registration number)

26
Norman F. Oblon, Reg. No. 24,618 ; Marvin J. Spivak, Reg. No. 24,913 ; C. Irvin McClelland, Reg. No. 21,124 ; Gregory J. Maier, Reg. No. 25,599 ; Arthur I. Neustadt, Reg. No. 24,854 ; Richard D. Kelly, Reg. No. 27,757 ; James D. Hamilton, Reg. No. 28,421 ; Eckhard H. Kuesters, Reg. No. 28,870 ; Robert T. Pous, Reg. No. 29,099 ; Charles L. Gholz, Reg. No. 26,395 ; William E. Beaumont, Reg. No. 30,996 ; Jean-Paul Lavalleye, Reg. No. 31,451 ; Stephen G. Baxter, Reg. No. 34,884 ; Richard L. Treanor, Reg. No. 36,379 ; Stephen P. Weihrouh, Reg. No. 32,829 ; John T. Goolkasian, Reg. No. 26,142 ; Richard L. Cinn, Reg. No. 34,305 ; Stephen E. Lipman, Reg. No. 30,011 ; Carl E. Shlier, Reg. No. 34,426 ; James J. Kubaski, Reg. No. 34,648 ; Richard A. Neifeld, Reg. No. 35,299 ; J. Dereck Mason, Reg. No. 35,270 ; Surinder Sachar, Reg. No. 34,423 ; Christina M. Gadiano, Reg. No. 37,628 ; Jeffrey B. McIntyre, Reg. No. 36,867 ; William T. Enos, Reg. No. 33,128 ; Michael E. McCabe, Jr., Reg. No. 37,182 ; Bradley D. Lytle, Reg. No. 40,073 ; and Michael R. Asey, Reg. No. 40,294, with full powers of substitution and revocation.

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Direct Telephone calls to : (name and telephone number)

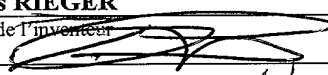
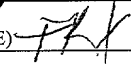
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1- Nom complete de l'unique ou premier inventeur Patrick M. ALLIEL		Full name of sole or first inventor	
Signature de l'inventeur <i>Patrick M. Alliel</i>		Inventor's signature	
Date <u>26/12/2000</u>		Date	
Domicile F-92140 Clamart (FRANCE)		Residence	
Nationalité Française		Citizenship	
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2- Nom complete du second co-inventeur, le cas echeant Jean-Pierre PERIN		Full name of second joint inventor, if any	
Signature de l'inventeur <i>Jean-Pierre Perin</i>		Second inventor's signature	
Date <u>27 Dec 2000</u>		Date	
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Nationalité Française		Citizenship	
Adresse Postale 182, rue d'Aulnay F-92350 Le Plessis-Robinson (FRANCE)		Post Office Address	

(Fournier les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

French Language Declaration

Nom complete du troisième co-inventeur, le cas échéant		Full name of third joint inventor, if any	
François RIEGER Signature de l'inventeur 		Third inventor's signature _____ Date _____	
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Nationalité Française		Citizenship	
Adresse Postale 38 bis, boulevard de la République 92100 Boulogne (FRANCE)		Post Office Address	
Nom complete du quatrième co-inventeur, le cas échéant		Full name of fourth joint inventor, if any	
Signature de l'inventeur _____ Date _____		Fourth inventor's signature _____ Date _____	
Domicile		Residence	
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Nom complete du cinquième co-inventeur, le cas échéant		Full name of fifth joint inventor, if any	
Signature de l'inventeur _____ Date _____		Fifth inventor's signature _____ Date _____	
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Nom complete du sixième co-inventeur, le cas échéant		Full name of sixth joint inventor, if any	
Signature de l'inventeur _____ Date _____		Sixth inventor's signature _____ Date _____	
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(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

528 Rec'd PCT/PTO 26 DEC 2000

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<210> 7
 <211> 1216
 <212> ADN
 <213> Homo sapiens

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<400> 7
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<210> 8
 <211> 976
 <212> ADN
 <213> Homo sapiens

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<400> 8
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gaattcctaa cttccaaagg aacacctatc aaacatcagg aagccattag gatattatta 240
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<210> 9
 <211> 942
 <212> ADN
 <213> Homo sapiens

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<400> 9
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gacacagaaa gtcaaaaaaa aagtttaagaa gaaaggaaaa gacaaagaag aagtcgaaga 240
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942

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<210> 10
 <211> 1375
 <212> ADN
 <213> Homo sapiens

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<400> 10
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10

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<210> 11
 <211> 944
 <212> ADN
 <213> Homo sapiens

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aaaagtatta cagaatcagg aagaagccat ctataccaat tctaagttaa tatggactga 240
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<210> 12
 <211> 963
 <212> ADN
 <213> Homo sapiens

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<400> 12
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tggaagatcc ttctatattt gcctcccac caactggaca ggaacttgta ctttagccta 240
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11

<210> 13
 <211> 1362
 <212> ADN
 <213> Homo sapiens

<400> 13
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<210> 14
 <211> 945
 <212> ADN
 <213> Homo sapiens

<400> 14
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12

<210> 15
 <211> 939
 <212> ADN
 <213> Homo sapiens

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<210> 16
 <211> 979
 <212> ADN
 <213> Homo sapiens

<400> 16
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<210> 17
 <211> 1774
 <212> ADN
 <213> Homo sapiens

<400> 17
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<210> 18

<211> 938

<212> ADN

<213> Homo sapiens

<400> 18

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gtttttattag	tagcaaaagaa	aaattaaaaat	cccaaaactta	caagggttttc	aactaaaagt	300
tgccaaaagt	taacagtgtta	acatgtatta	tcctactatc	acacactctc	aaaggatttc	360
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tcaactaaca	acttctactg	aggacacctg	gactgaccca	ctggcccttt	cactggccta	840
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<212> ADN

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15

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cttctaatag agctataaca ctcaccgcat ggcccaaggt tccattcctt gaatccataa 660
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caa caa gtt ctt aaa aca tta caa gga acc tat ccc tga gaa gag gga 96
Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Glu Glu Gly
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aaa gaa cta ttc cac cct tgt gac atg gta tta gtc aag tcc ctt ccc 144
Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
          35          40          45

tct aat tcc cca tcc cta gat aca tcc tgg gaa gga ccc tac cca gtc 192
Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
          50          55          60

att tta tct acc cca act gcg gtt aaa gtg gct gga gtg gag tct tgg 240
Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
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Ile His His Thr Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
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aat cca gga gac aac gct agc tat tcc tgt gaa cct cta gag gat ttg 336
Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
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cgc ctg ctc ttc aaa caa caa cca gga gga aag taa cta aaa tca taa 384
Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys Leu Lys Ser
          115          120          125

atc ccc atg gcc ctc cct tat cat att ttt ctc ttt act gtt ctt tta 432
Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
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ccc tct ttc act ctc act gca ccc cct cca tgc cgc tgt atg acc agt 480
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Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe	
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Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu	
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Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro	
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Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu	
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Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr	
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Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu	
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cgt acc cat act cgc ctg gta agc cta ttt aat acc acc ctc act ggg	912
Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly	
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Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu	
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ccc ctg aac ttc agg cca tat gtt tca atc cct gta cct gaa caa tgg	1008
Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp	
325 330 335	
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Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro	
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ctt gtt tcc aat ctg gaa ata acc cat acc tca aac ctc acc tgt gta	1104
Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val	
355 360 365	
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Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp	
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Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser	
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Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu	
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Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val	
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Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu	
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Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn	
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Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val	
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Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu	
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Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser	
595 600 605	

18

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act aag atc tac cgc aga ccc ctg gac cgg cct gct agc cca cga tct 1920
 Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
 625 630 635 640

gat gtt aat gac atc aaa ggc acc cct cct gag gaa atc tca gct gca 1968
 Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
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caa cct cta cta cgc ccc aat tca gca gga agc agt tag agc ggt cgt 2016
 Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser Ser Gly Arg
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<212> PRT

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Tyr Pro Val Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val
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Glu Ser Trp Ile His His Thr
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<213> Homo sapiens

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Gln Gln Pro Gly Gly Lys
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<212> PRT

<213> Homo sapiens

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 20 25 30

Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
 35 40 45

Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
 50 55 60

Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
 65 70 75 80

Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
 85 90 95

Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
 100 105 110

Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
 115 120 125

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
 130 135 140

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
 145 150 155 160

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
 165 170 175

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
 180 185 190

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
 195 200 205

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
 210 215 220

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Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
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 245 250 255
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 260 265 270
 Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
 275 280 285
 Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
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 Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
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 Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
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 405 410 415
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 420 425 430
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 Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
 485 490 495
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 Leu Ser Phe His Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
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 Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
 35 40 45

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 Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
 50 55 60

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 65 70 75 80

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 85 90 95

cca gcc aga gtg cat gtg cct ttt tct ctc cca gac tta aag caa ata 336
 Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
 100 105 110

aaa aca gac tta ggt aaa ttc tca gat aac cct gat ggc tat att gat 384
 Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
 115 120 125

22

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Ile Thr Ala Ala Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val	
165 170 175	
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Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile	
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Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu	
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acc cta ttg aac ttg gca acc tcg gtt ttt tat aat aga gat cag gag	960
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1080

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 35 40 45
 Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn Ile Pro Gln Leu
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 <211> 79
 <212> PRT
 <213> Homo sapiens

<400> 31
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 Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile Lys Thr Asp Leu Gly
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 Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu
 35 40 45
 Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile Met Ser Leu Leu Asn
 50 55 60
 Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr Ile Thr Ala Ala
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<400> 33
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 35 40 45
 Met Met Ser Thr Ile Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe
 50 55 60
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 65 70 75 80
 Asp Ser Ser Glu Gly Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln
 85 90 95
 Ser Ala Ala Asp Ile Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro
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 50 55 60
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 65 70 75 80
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 Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
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 Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys Xaa Leu Lys Ser Xaa
 115 120 125
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 210 215 220
 Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
 225 230 235 240
 Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
 245 250 255

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
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 Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
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 Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
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 Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
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 Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
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 Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
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 Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
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 Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
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 Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
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 Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
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 Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
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 Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
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 Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
 625 630 635 640
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 <213> Homo sapiens

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 35 40 45
 Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
 50 55 60
 Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
 65 70 75 80
 Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
 85 90 95
 Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
 100 105 110
 Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
 115 120 125
 Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile
 130 135 140

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 Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly Gln
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 Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu
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 Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile
 225 230 235 240
 Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg
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 Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly
 260 265 270
 Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile
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 Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu
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 Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg Phe
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Ser Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met
50 55 60
Val Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala
65 70 75 80
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Gly Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln
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Ile Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile
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130 135 140
Ile Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala
145 150 155 160
Thr Ile Thr Ala Ala Xaa Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln
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Val Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly
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Gln Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu
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His Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly
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Leu Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr
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245 250 255

Arg Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu
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 Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg
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<213> Homo sapiens

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 Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Glu Glu Gly
 20 25 30
 aaa gaa cta ttc cac cct tgt gac atg gta tta gtc aag tcc ctt ccc 144
 Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
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 Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
 50 55 60
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Ile	His	His	Thr		Val	Lys	Ser	Trp	Ile	Leu	Pro	Lys	Glu	Pro	Glu	
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Asn	Pro	Gly	Asp	Asn	Ala	Ser	Tyr	Ser	Cys	Glu	Pro	Leu	Glu	Asp	Leu	
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Arg	Leu	Leu	Phe	Lys	Gln	Gln	Pro	Gly	Gly	Lys		Leu	Lys	Ser		
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Ile	Pro	Met	Ala	Leu	Pro	Tyr	His	Ile	Phe	Leu	Phe	Thr	Val	Leu	Leu	
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Lys	His	Val	Lys	Glu	Val	Ile	Ser	Gln	Leu	Thr	Arg	Val	His	Gly	Thr	
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ctc	cat	gag	gtc	tcg	gcc	caa	aac	cct	act	aac	tgt	tgg	ata	tgc	ctc	960
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	Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser			
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	Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala			
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	Tyr Pro Val Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val			
	35	40	45	
	Glu Ser Trp Ile His His Thr			
	50	55		
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	Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu Asn Pro Gly Asp Asn			

1 5 10 15
Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu Arg Leu Leu Phe Lys
20 25 30
Gln Gln Pro Gly Gly Lys
35
<210> 26 <211> 540 <212> PRT <213> Homo sapiens <400> 26
Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
1 5 10 15
Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
20 25 30
Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
35 40 45
Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
50 55 60
Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
65 70 75 80
Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
85 90 95
Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
100 105 110
Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
115 120 125
Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
130 135 140
Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
145 150 155 160
Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
165 170 175
Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
180 185 190
Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp

195 200 205

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
210 215 220

Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
225 230 235 240

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
245 250 255

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
260 265 270

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
275 280 285

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
290 295 300

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
305 310 315 320

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
325 330 335

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
340 345 350

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
355 360 365

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn
370 375 380

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
385 390 395 400

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
405 410 415

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
420 425 430

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
435 440 445

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
450 455 460

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
465 470 475 480

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
485 490 495

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
500 505 510

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
515 520 525

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser
530 535 540

<210> 27 <211> 15 <212> PRT <213> Homo sapiens <400> 27

Ser Gly Arg Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys
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<210> 28 <211> 1080 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)..(1080)
<223>

<400> 28

acc tct ttt gta gaa aag gca aat gga gtg aag tgc cat aag tac aaa 48
Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
5 10 15

tct tct ttt cat taa gag aca act cac aat tat gta aaa agt gtg att 96
Leu Ser Phe His Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
20 25 30

tat gcc cta cag gaa gcc ttc aga gtc tac ctc cct atc cca gca tcc 144
Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
35 40 45

ccg act cct tcc cca act aat aag gac ccc cct tca acc caa atg gtc 192
Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
50 55 60

caa aag gag ata gac aaa agg gta aac agt gaa cca aag agt gcc aat 240
Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
65 70 75

att ccc caa tta tga ccc ctc caa gca gtg gga gga aga gaa ttc ggc 288
Ile Pro Gln Leu Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
80 85 90

cca gcc aga gtg cat gtg cct ttt tct ctc cca gac tta aag caa ata 336
Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
95 100 105 110

aaa aca gac tta ggt aaa ttc tca gat aac cct gat ggc tat att gat Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp 115 120 125	384
gtt tta caa ggg tta gga caa ttc ttt gat ctg aca tgg aga gat ata Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile 130 135 140	432
atg tca ctg cta aat cag aca cta acc cca aat gag aga agt gcc acc Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr 145 150 155	480
ata act gca gcc tga gag ttt ggc gat ctc tgg tat ctc agt cag gtc Ile Thr Ala Ala Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val 160 165 170	528
aat gat agg atg aca aca gag gaa aga gaa tga ttc ccc aca ggc cag Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Phe Pro Thr Gly Gln 175 180 185	576
cag gca gtt ccc agt cta gac cct cat tgg gac aca gaa tca gaa cat Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu His 190 195 200	624
aga gat tgg tgc tgc aga cat ttg cta act tgt gtg cta gaa gga cta Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu 205 210 215 220	672
agg aaa act agg aag aag tct atg aat tac tca atg atg tcc acc ata Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile 225 230 235	720
aca cag gga agg gaa gaa aat cct act gcc ttt ctg gag aga cta agg Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg 240 245 250	768
gag gca ttg agg aag cgt gcc tct ctg tca cct gac tct tct gaa ggc Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly 255 260 265	816
caa cta atc tta aag cgt aag ttt atc act cag tca gct gca gac att Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile 270 275 280	864
aga aaa aaa ctt caa aag tct gcc gta ggc ccg gag caa aac tta gaa Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu 285 290 295 300	912
acc cta ttg aac ttg gca acc tcg gtt ttt tat aat aga gat cag gag Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu 305 310 315	960
gag cag gcg gaa cag gac aaa cgg gat taa aaa aaa ggc cac cgc ttt Glu Gln Ala Glu Gln Asp Lys Arg Asp Lys Lys Gly His Arg Phe 320 325 330	1008
agt cat gac cct cag gca agt gga ctt tgg agg ctc tgg aaa agg gaa Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg Glu 335 340 345	1056
aag ctg ggc aaa ttg aat gcc taa Lys Leu Gly Lys Leu Asn Ala	1080

350

<210> 29 <211> 20 <212> PRT <213> Homo sapiens <400> 29

Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
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Leu Ser Phe His
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<210> 30 <211> 63 <212> PRT <213> Homo sapiens <400> 30

Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile Tyr Ala Leu Gln Glu
1 5 10 15

Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser Pro Thr Pro Ser Pro
20 25 30

Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val Gln Lys Glu Ile Asp
35 40 45

Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn Ile Pro Gln Leu
50 55 60

<210> 31 <211> 79 <212> PRT <213> Homo sapiens <400> 31

Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly Pro Ala Arg Val His
5 10 15

Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile Lys Thr Asp Leu Gly
20 25 30

Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu
35 40 45

Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile Met Ser Leu Leu Asn
50 55 60

Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr Ile Thr Ala Ala
65 70 75

<210> 32 <211> 21 <212> PRT <213> Homo sapiens <400> 32

Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val Asn Asp Arg Met Thr
1 5 10 15

Thr Glu Glu Arg Glu
20

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<210> 33 <211> 142 <212> PRT <213> Homo sapiens <400> 33
Phe Pro Thr Gly Gln Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp
1          5          10          15
Thr Glu Ser Glu His Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys
          20          25          30
Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser
          35          40          45
Met Met Ser Thr Ile Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe
          50          55          60
Leu Glu Arg Leu Arg Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro
          65          70          75          80

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Asp Ser Ser Glu Gly Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln
          85          90          95
Ser Ala Ala Asp Ile Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro
          100          105          110
Glu Gln Asn Leu Glu Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr
          115          120          125
Asn Arg Asp Gln Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp
          130          135          140

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<210> 34 <211> 29 <212> PRT <213> Homo sapiens <400> 34
Lys Lys Gly His Arg Phe Ser His Asp Pro Gln Ala Ser Gly Leu Trp
1          5          10          15
Arg Leu Trp Lys Arg Glu Lys Leu Gly Lys Leu Asn Ala
          20          25

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<210> 35 <211> 685 <212> PRT <213> Homo sapiens <220> <221> misc_feature <222>
(29)..(29) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (85)..(85) <223> Xaa is any amino acid
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<220> <221> misc_feature <222> (128)..(128) <223> Xaa is any amino acid
<220> <221> misc_feature <222> (669)..(669) <223> Xaa is any amino acid
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<400> 35

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Pro Lys Thr Ala Asn Leu Val Ala Asp Ile Thr Ser Leu Ala Lys Tyr
 1 5 10 15
 Gln Gln Val Leu Lys Thr Leu Gln Gly Thr Tyr Pro Xaa Glu Glu Gly
 20 25 30
 Lys Glu Leu Phe His Pro Cys Asp Met Val Leu Val Lys Ser Leu Pro
 35 40 45
 Ser Asn Ser Pro Ser Leu Asp Thr Ser Trp Glu Gly Pro Tyr Pro Val
 50 55 60
 Ile Leu Ser Thr Pro Thr Ala Val Lys Val Ala Gly Val Glu Ser Trp
 65 70 75 80
 Ile His His Thr Xaa Val Lys Ser Trp Ile Leu Pro Lys Glu Pro Glu
 85 90 95
 Asn Pro Gly Asp Asn Ala Ser Tyr Ser Cys Glu Pro Leu Glu Asp Leu
 100 105 110
 Arg Leu Leu Phe Lys Gln Gln Pro Gly Gly Lys Xaa Leu Lys Ser Xaa
 115 120 125
 Ile Pro Met Ala Leu Pro Tyr His Ile Phe Leu Phe Thr Val Leu Leu
 130 135 140
 Pro Ser Phe Thr Leu Thr Ala Pro Pro Pro Cys Arg Cys Met Thr Ser
 145 150 155 160
 Ser Ser Pro Tyr Gln Glu Phe Leu Trp Arg Met Gln Arg Pro Gly Asn
 165 170 175
 Ile Asp Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Thr Pro Thr Phe
 180 185 190
 Thr Ala His Thr His Met Pro Arg Asn Cys Tyr His Ser Ala Thr Leu
 195 200 205
 Cys Met His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro
 210 215 220
 Ser Cys Pro Gly Gly Leu Gly Val Thr Val Cys Trp Thr Tyr Phe Thr
 225 230 235 240
 Gln Thr Gly Met Ser Asp Gly Gly Gly Val Gln Asp Gln Ala Arg Glu
 245 250 255

Lys His Val Lys Glu Val Ile Ser Gln Leu Thr Arg Val His Gly Thr
 260 265 270

Ser Ser Pro Tyr Lys Gly Leu Asp Leu Ser Lys Leu His Glu Thr Leu
 275 280 285

Arg Thr His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Gly
 290 295 300

Leu His Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Ile Cys Leu
 305 310 315 320

Pro Leu Asn Phe Arg Pro Tyr Val Ser Ile Pro Val Pro Glu Gln Trp
 325 330 335

Asn Asn Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro
 340 345 350

Leu Val Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val
 355 360 365

Lys Phe Ser Asn Thr Thr Tyr Thr Thr Asn Ser Gln Cys Ile Arg Trp
 370 375 380

Val Thr Pro Pro Thr Gln Ile Val Cys Leu Pro Ser Gly Ile Phe Phe
 385 390 395 400

Val Cys Gly Thr Ser Ala Tyr Arg Cys Leu Asn Gly Ser Ser Glu Ser
 405 410 415

Met Cys Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu
 420 425 430

Gln Asp Leu Tyr Ser Tyr Val Ile Ser Lys Pro Arg Asn Lys Arg Val
 435 440 445

Pro Ile Leu Pro Phe Val Ile Gly Ala Gly Val Leu Gly Ala Leu Gly
 450 455 460

Thr Gly Ile Gly Gly Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu
 465 470 475 480

Ser Gln Glu Leu Asn Gly Asp Met Glu Arg Val Ala Asp Ser Leu Val
 485 490 495

Thr Leu Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn

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      500                      505                      510

Arg Arg Ala Leu Asp Leu Leu Thr Ala Glu Arg Gly Gly Thr Cys Leu
   515                      520                      525

Phe Leu Gly Glu Glu Cys Cys Tyr Tyr Val Asn Gln Ser Gly Ile Val
   530                      535                      540

Thr Glu Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Arg Arg Ala Glu
   545                      550                      555                      560

Glu Leu Arg Asn Thr Gly Pro Trp Gly Leu Leu Ser Gln Trp Met Pro
   565                      570                      575

Trp Ile Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Leu Leu Leu
   580                      585                      590

Leu Phe Gly Pro Cys Ile Phe Asn Leu Leu Val Asn Phe Val Ser Ser
   595                      600                      605

Arg Ile Glu Ala Val Lys Leu Gln Met Glu Pro Lys Met Gln Ser Lys
   610                      615                      620

Thr Lys Ile Tyr Arg Arg Pro Leu Asp Arg Pro Ala Ser Pro Arg Ser
   625                      630                      635                      640

Asp Val Asn Asp Ile Lys Gly Thr Pro Pro Glu Glu Ile Ser Ala Ala
   645                      650                      655

Gln Pro Leu Leu Arg Pro Asn Ser Ala Gly Ser Ser Xaa Ser Gly Arg
   660                      665                      670

Arg Pro Thr Ser Pro Thr Ala Leu Arg Phe Ser Cys Xaa
   675                      680                      685

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<210> 36 <211> 360 <212> PRT <213> Homo sapiens <220> <221> misc_feature <222>
(21)..(21) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (85)..(85) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (165)..(165) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (187)..(187) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (330)..(330) <223> Xaa is any amino acid

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<220> <221> misc_feature <222> (360)..(360) <223> Xaa is any amino acid

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<400> 36

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Thr Ser Phe Val Glu Lys Ala Asn Gly Val Lys Cys His Lys Tyr Lys
 1 5 10 15
 Leu Ser Phe His Xaa Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
 20 25 30
 Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Pro Ala Ser
 35 40 45
 Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met Val
 50 55 60
 Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala Asn
 65 70 75 80
 Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe Gly
 85 90 95
 Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln Ile
 100 105 110
 Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp
 115 120 125
 Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp Ile
 130 135 140
 Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala Thr
 145 150 155 160
 Ile Thr Ala Ala Xaa Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln Val
 165 170 175
 Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly Gln
 180 185 190
 Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu His
 195 200 205
 Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly Leu
 210 215 220
 Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr Ile
 225 230 235 240
 Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu Arg
 245 250 255

Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu Gly
 260 265 270

Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp Ile
 275 280 285

Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu Glu
 290 295 300

Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln Glu
 305 310 315 320

Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg Phe
 325 330 335

Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg Glu
 340 345 350

Lys Leu Gly Lys Leu Asn Ala Xaa
 355 360

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 ggaccataga ggacactcca ggacta 26

<210> 38 <211> 25 <212> DNA <213> Homo sapiens <400> 38
 cctcagtcct gctgctggat catct 25

<210> 39 <211> 27 <212> DNA <213> Homo sapiens <400> 39
 cctccaagca gtgggaggaa gagaatt 27

<210> 40 <211> 28 <212> DNA <213> Homo sapiens <400> 40
 ccttccctgt gttattgtgg acatcatt 28

<210> 41 <211> 30 <212> DNA <213> Homo sapiens <400> 41
 ggaagaagtc tatgaattat tcaatgatgt 30

<210> 42 <211> 27 <212> DNA <213> Homo sapiens <400> 42
 gggacacaga atcagaacat ggagatt 27

<210> 43 <211> 27 <212> DNA <213> Homo sapiens <400> 43
 gccttcagaa gagtcagggtg acagaga 27

<210> 44 <211> 25 <212> DNA <213> Homo sapiens <400> 44
 gagcctccaa agtccacttg cctga 25

<210> 45 <211> 29 <212> DNA <213> Homo sapiens <400> 45

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<210> 47 <211> 28 <212> DNA <213> Homo sapiens <400> 47
ccaagacagc caacttagtt gcagacat 28

<210> 48 <211> 28 <212> DNA <213> Homo sapiens <400> 48
ggacgctgca ttctccatag aaactcct 28

<210> 49 <211> 29 <212> DNA <213> Homo sapiens <400> 49
gcaatactac atacacaacc aactcccaa 29

<210> 50 <211> 26 <212> DNA <213> Homo sapiens <400> 50
gggggaggca tatccaacag ttagta 26

<210> 51 <211> 30 <212> DNA <213> Homo sapiens <400> 51
ccatctacac tgaacaagat ttatacactt 30

<210> 52 <211> 28 <212> DNA <213> Homo sapiens <400> 52
atgccagta cctagtgcac ctagcact 28

<210> 53 <211> 31 <212> DNA <213> Homo sapiens <400> 53
gaataacaac gtagagcaga ggagcttcga a 31

<210> 54 <211> 28 <212> DNA <213> Homo sapiens <400> 54
gcccaagat gcagtccaag actaagat 28

<210> 55 <211> 27 <212> DNA <213> Homo sapiens <400> 55
gcgtagtaga gggtgtgcag ctgagat 27

<210> 56 <211> 27 <212> DNA <213> Homo sapiens <400> 56
cccttaccaa gagtttctat ggagaat 27

<210> 57 <211> 27 <212> DNA <213> Homo sapiens <400> 57
accgctctaa ctgcttcctg ctgaatt 27

<210> 58 <211> 420 <212> PRT <213> Homo sapiens <220> <221> misc_feature <222>
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<220> <221> misc_feature <222> (188)..(188) <223> Xaa is any amino acid
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 <220> <221> misc_feature <222> (413)..(413) <223> Xaa is any amino acid
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 1 5 10 15

Leu Ser Phe His Xaa Glu Thr Thr His Asn Tyr Val Lys Ser Val Ile
 20 25 30

Tyr Ala Leu Gln Glu Ala Phe Arg Val Tyr Leu Pro Ile Leu Pro Ala
 35 40 45

Ser Pro Thr Pro Ser Pro Thr Asn Lys Asp Pro Pro Ser Thr Gln Met
 50 55 60

Val Gln Lys Glu Ile Asp Lys Arg Val Asn Ser Glu Pro Lys Ser Ala
 65 70 75 80

Asn Ile Pro Gln Leu Xaa Pro Leu Gln Ala Val Gly Gly Arg Glu Phe
 85 90 95

Gly Pro Ala Arg Val His Val Pro Phe Ser Leu Pro Asp Leu Lys Gln
 100 105 110

Ile Lys Thr Asp Leu Gly Lys Phe Ser Asp Asn Pro Asp Gly Tyr Ile
 115 120 125

Asp Val Leu Gln Gly Leu Gly Gln Phe Phe Asp Leu Thr Trp Arg Asp
 130 135 140

Ile Met Ser Leu Leu Asn Gln Thr Leu Thr Pro Asn Glu Arg Ser Ala
 145 150 155 160

Thr Ile Thr Ala Ala Xaa Glu Phe Gly Asp Leu Trp Tyr Leu Ser Gln
 165 170 175

Val Asn Asp Arg Met Thr Thr Glu Glu Arg Glu Xaa Phe Pro Thr Gly
 180 185 190

Gln Gln Ala Val Pro Ser Leu Asp Pro His Trp Asp Thr Glu Ser Glu
 195 200 205
 His Gly Asp Trp Cys Cys Arg His Leu Leu Thr Cys Val Leu Glu Gly
 210 215 220
 Leu Arg Lys Thr Arg Lys Lys Ser Met Asn Tyr Ser Met Met Ser Thr
 225 230 235 240
 Ile Thr Gln Gly Arg Glu Glu Asn Pro Thr Ala Phe Leu Glu Arg Leu
 245 250 255
 Arg Glu Ala Leu Arg Lys Arg Ala Ser Leu Ser Pro Asp Ser Ser Glu
 260 265 270
 Gly Gln Leu Ile Leu Lys Arg Lys Phe Ile Thr Gln Ser Ala Ala Asp
 275 280 285
 Ile Arg Lys Lys Leu Gln Lys Ser Ala Val Gly Pro Glu Gln Asn Leu
 290 295 300
 Glu Thr Leu Leu Asn Leu Ala Thr Ser Val Phe Tyr Asn Arg Asp Gln
 305 310 315 320
 Glu Glu Gln Ala Glu Gln Asp Lys Arg Asp Xaa Lys Lys Gly His Arg
 325 330 335
 Phe Ser His Asp Pro Gln Ala Ser Gly Leu Trp Arg Leu Trp Lys Arg
 340 345 350
 Glu Lys Leu Gly Lys Leu Asn Ala Xaa Xaa Gly Leu Leu Pro Val Arg
 355 360 365
 Ser Thr Arg Thr Leu Xaa Lys Arg Leu Ser Lys Xaa Lys Xaa Ala Ala
 370 375 380
 Pro Ser Ser Met Pro Leu Ile Ser Arg Glu Ser Leu Glu Gly Pro Leu
 385 390 395 400
 Pro Gln Gly Thr Lys Val Leu Xaa Val Arg Ser His Xaa Pro Asp Ser
 405 410 415
 Ser Ser Arg Thr
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<210> 59 <211> 32 <212> DNA <213> Homo sapiens <400> 59

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<210> 60 <211> 32 <212> DNA <213> Homo sapiens <400> 60
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<210> 61 <211> 1740 <212> DNA <213> Homo sapiens <400> 61
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gcaggccagt ccaggggtcc gcggtagatc ttagtcatgg actgcatctg gggctccatt 180
tgaagaacca tttgtagttt tacagcttcg attctggaag agacaaacgt aacaaggagg 240
ttaaagatac aaggattgaa atgtacggcc tgaagtgcag gggcatatga gtgtgggcgg 300
tgcaagtggg gtttccttta gaaaaactcc gatacaatag ggcatcaata tttctaggaa 360
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